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VITAMIN B_{12} THERAPY IN MEGALOBLASTIC ANEMIA OF INFANCY

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A SEVERE anemia occurring in infants under the age of 18 months with megalobastic blood formation in the bone marrow has been recognized with increasing frequency in recent years.[1-6, 12, 13] Infection and feeding difficulties predisposing to dietary inadequacy are common antecedents. The anemia responds specifically to liver extract or to pteroylgutamic acid therapy.[2, 3, 5, 9, 12, 13]

The clinical findings in different cases are highly variable. The anemia may be normochromic and normocytic, or macrocytic. The red blood cells usually vary greatly in size and in shape and show evidence of disturbed maturation. There is a tendency toward leucopenia, neutropenia, and thrombopenia. Some infants are jaundiced. Free hydrochloric acid may or may not be present in the gastric contents. Examination of the bone marrow is usually necessary to establish the diagnosis.[12] Injections of liver extract or pteroylglutamic acid given orally or parenterally are effective therapeutically, although the rate of response is variable. A reticulocytosis is induced which usually reaches a maximum in from six to eight days and a normal type of erythropoiesis is restored in the bone marrow.[12] After the anemia is once corrected, specific therapy generally does not need to be continued.

Rickes and co-workers[7] have recently isolated from liver a new crystalline compound containing cobalt which in microgram quantities induces hematologic and clinical responses in patients with pernicious anemia.[8, 10, 11] Preliminary estimates indicate that one microgram of this substance, designated vitamin B_{12}, is equivalent to 1 U.S.P. unit of liver extract. We have treated two infants with megaloblastic anemia with vitamin B_{12}. Their case histories follow.

CASE REPORTS

CASE 1, J. B. J., C-43272.—This 11-month-old Negro girl was first brought to the Pediatric Clinic of Duke Hospital on Sept. 7, 1948, with the chief complaints of weakness, constipation, and colic.

At birth the infant appeared to be healthy. After the age of one month she cried a great deal, nursed poorly, and appeared to have considerable colicky

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TABLE I. HEMATOLOGIC FINDINGS IN CASE 1, J. B. J., C-43272

DATE 1948	Hb. (GM. PER 100 C.C.)	RBC (MILLIONS PER C.MM.)	WBC	HEMATOCRIT	MEAN CORPUSCULAR VOLUME (CU.M.)	RETICULOCYTE (PER CENT)	PLATELETS	DIFFERENTIAL WBC AND THERAPY
9/15	3.2	1.1	20,000	10	92	7.4	27,000	Segmented polymorphonuclears 31, stabs 2, metamyelocytes 1, myelocytes 3, myeloblasts 1, lymphocytes 48, monocytes 2, eosinophiles 12, nucleated RBC 12/100 WBC.
9/16	*Tibial Marrow:* Segmented polymorphonuclear 1.75, stabs 9.5, metamyelocytes 2.5, myelocytes 6.75, myeloblasts 0.25, lymphocytes 3, eosinophiles 8, plasma cells 0.25, acidophilic megaloblasts 23, basophilic megaloblasts 35.5, promegaloblasts 9.5. Leucocyte: nucleated red cell ratio = 1:2.2							
9/17	2.9	0.92	26,000	8.5	92	5.8	34,000	Vitamin B_{12}, 0.002 mg.
9/18						8.7		
9/19						10.5		
9/20	3.5	1.1				26.8		
9/21	4.5	1.3				46.1		
9/22	5.4	1.5				53.9		
9/23	6.5	2.0				49.5		
9/24	6.6	2.2	19,000	24	108	69.1		
9/25						24.6		
	Tibial Marrow: Segmented polymorphonuclears 11, stabs 23, metamyelocytes 5.5, myelocytes 5, myeloblasts 0.5, lymphocytes 0.5, eosinophiles 6, plasma cells 0.5, acidophilic megaloblasts 25, basophilic megaloblasts 20, promegaloblasts 3. Leucocyte: nucleated red cell ratio = 1.1:1							
9/26						12.3		
9/27						10.9		
9/28	7.8	2.6	17,150	28	107	12.0		
9/29						12.2		
9/30						13.7		
	Tibial Marrow: Segmented polymorphonuclears 13, stabs 21, metamyelocytes 4, myelocytes 5, myeloblasts 0.5, lymphocytes 2.5, eosinophiles 5.5, acidophilic normoblasts 31.5, basophilic normoblasts 14, pronormoblasts 3. Leucocyte: nucleated red cell ratio = 1.1:1							
10/1	7.8	2.8	13,350	30	104	13.5	Abundant	Segmented polymorphonuclears 73, lymphocytes 16, monocytes 3, eosinophiles 8, nucleated RBC 2/100 WBC.
10/22	10.0	3.2	15,050	30.5	94	1.3	Abundant	Segmented polymorphonuclears 61, lymphocytes 27, monocytes 6, eosinophiles 6.
12/8	12.2	4.0	11,650	37.0	93	0.8		

abdominal pain. Bowel movements became infrequent. Her abdominal pain seemed to be worse when she was given cereal or vegetables. Consequently her diet was restricted to breast milk without the addition of solid foods, orange juice, or cod liver oil. During the first six months her growth and development appeared to be normal. Subsequent development was slow, and she made no attempt to crawl or walk. Two weeks before being brought to the clinic she became particularly irritable, fretful, and slightly febrile. The family physician prescribed powders and injected penicillin intramuscularly, but there was no symptomatic benefit.

Four older siblings and the parents were healthy.

Physical examination in the out-patient clinic showed a moderately well-developed and well-nourished Negro infant who was very fretful and irritable. The rectal temperature was 37.5° C. and the weight 13½ pounds. The mucous membranes and nail beds were very pale. There was no jaundice. The heart was enlarged. The liver was palpable 2 cm. below the right costal margin. Serologic tests for syphilis and a test for red cell sickling were negative. The hemoglobin was 4 Gm. per 100 c.c., and the white blood count 8,000. The anemia was thought to be the result of general nutritional and iron deficiency. An evaporated milk formula supplemented with cereal, egg yolk, a preparation containing vitamins B and C, and elixir of ferrous sulfate were prescribed. After one week at home on this regimen, there was no improvement. The infant was then admitted to the hospital for further study.

The physical findings were unchanged except for a new pustular lesion on the occiput measuring 1 by 2 cm. A catheterized urine specimen contained a trace of protein and ten to twenty white cells in the sediment. Urine cultures yielded hemolytic and nonhemolytic *Escherichia coli*. Tuberculin and histoplasmin skin tests were negative. The serum proteins were 6.1 Gm. per 100 c.c., and with albumin 3.9 Gm. and globulin 2.2 Gm. The nonprotein nitrogen was 26 mg. per 100 c.c. and the serum bilirubin 1.1 and 2.2 mg. on different occasions. A roentgenogram of the chest showed enlargement of the heart and clear lung fields. Roentgen examination of the intestinal tract and long bones showed no abnormalities. Gastric analysis showed free hydrochloric acid in the gastric contents.

Examination of the peripheral blood (Table I) showed a severe normochromic, normocytic anemia with leucocytosis and thrombopenia. The red blood cells were well colored and varied greatly in size and shape. Stippled red cells, huge basophilic macrocytes, nucleated red cells of large diameter and with immature nuclei, nonsegmented neutrophiles, neutrophilic myelocytes and myeloblasts were present in the circulating blood. Bone marrow aspirated from the tibia was very cellular and showed conspicuous megaloblastic development of the red and white cell series (Fig. 1, *A*). The erythroid elements were increased to predominate over the myeloid elements.

After admission to the hospital the infant remained listless, ate poorly, and vomited frequently. Parenteral fluids were administered but blood transfusions were withheld. Penicillin and sulfonamide therapy was given for the urinary tract infection which cleared in a few days. The blood values continued to fall and the infant became weaker and developed muscular twitching. She improved slightly when given oxygen therapy.

On the second hospital day a single dose of 0.002 mg. of vitamin B_{12} was given intramuscularly. The reticulocyte percentage rose two days later and reached a peak of 69.1 per cent on the seventh day. A second bone marrow examination at this time showed the marrow still extremely cellular with erythroid elements predominating. A suggestion of megaloblastic development was still present. Following the reticulocytosis there was rapid regeneration of blood (Table I). A third bone marrow examination thirteen days after the injection

of vitamin B_{12} showed normoblastic cellular development with very active red cell proliferation. The infant's condition improved rapidly with the gain in hemoglobin and red cell count, and when discharged two weeks after the vitamin B_{12} injection, she was active, playful, eating well, and able to sit alone in bed.

She was brought back to the clinic for follow-up examination three and ten weeks after returning home. She had continued to eat well and had gained weight steadily. The blood values were normal (Table I).

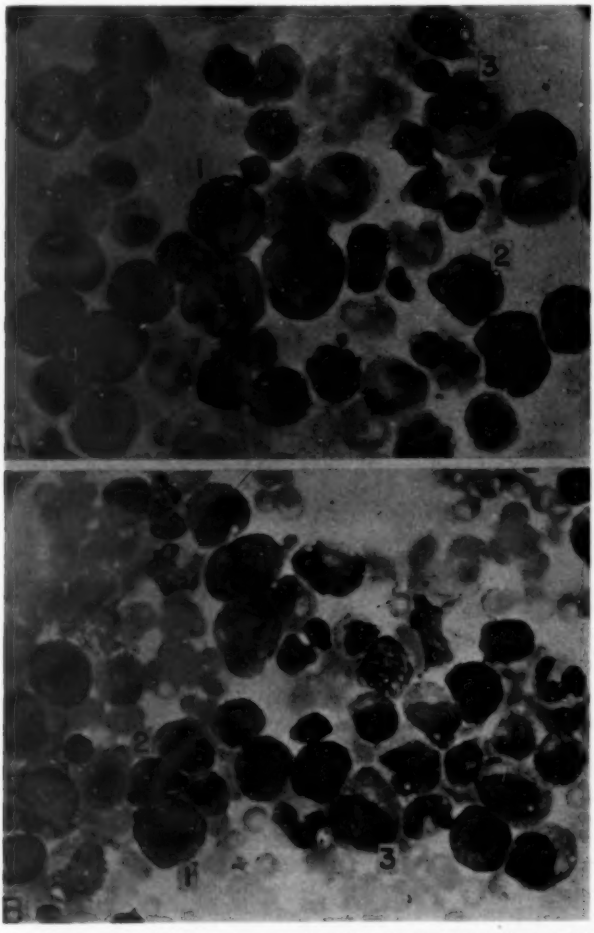

Fig. 1.—*A*, Photograph of bone marrow of patient in Case 1 before treatment (×625). *B*, Photograph of bone marrow of patient in Case 2 before treatment (×625). *1*, Promegaloblast; *2*, megaloblasts; *3*, giant metamyelocyte.

CASE 2, W. J. P., C-44538.—This 7-month-old white male infant was admitted to Duke Hospital on Sept. 22, 1948, having had swelling of the legs and generalized weakness for two months.

At birth the infant was healthy. He was fed a powdered milk formula with vitamin supplements. He grew well and weighed 14 pounds at the age of 14 weeks. About this time he developed a series of ulcerated lesions in his mouth and throat. He began to eat poorly and vomited frequently. It was necessary to admit him finally to the local hospital where anemia was discovered. He was given a blood transfusion and goat's milk was substituted for cow's milk in his formula. At home he was better for about three weeks but then again he began to eat poorly and lose weight. Swelling of his feet was noted from time to time.

The infant's parents and a 4-year-old brother were well.

Physical examination showed a scrawny, weak, irritable, and chronically ill infant weighing 11½ pounds. He was not jaundiced. There were no local abnormalities about the head, neck, or chest. The liver and spleen were not palpable. There was slight edema of both feet.

Urinalyses, stool examination, and serologic tests for syphilis were negative. The tuberculin and histoplasmin skin tests were negative. The fasting blood sugar was 90 mg. and the nonprotein nitrogen 25 mg. per 100 c.c. The serum bilirubin was not elevated. The serum proteins were 3.9 Gm. per 100 c.c. with albumin 2.0 Gm. and globulin 1.9 Gm. There was no free hydrochloric acid in the gastric contents after histamine injection. Roentgen examination of the chest, intestinal tract, skull, and long bones showed no definite abnormalities.

Examination of the peripheral blood showed a normocytic normochromic anemia (Table II). In the stained blood films the red cells varied moderately in size. Many were obviously macrocytic. The differential white cell count included a small number of nonsegmented neutrophiles. Bone marrow of high cellularity was aspirated from the tibia. In the stained films the predominant cells were large neutrophilic granulocytes showing maturation arrest at the late myelocyte stage. The erythroid elements had megaloblastic characteristics (Fig. 1, *B*).

The infant was given 0.002 mg. of vitamin B_{12} intramuscularly and a week later 0.005 mg. A transient reticulocytosis occurred on the ninth day of therapy but the bone marrow remained megaloblastic and the blood values continued to fall (Table II). He continued to vomit in spite of several changes in formula, and gradually became very weak and listless. On the twelfth day the vitamin B_{12} was increased to 0.002 mg. daily. Twenty grams of serum albumin were given intravenously during a four-day period. On the nineteenth day of antianemic therapy there was a second reticulocytosis which was better sustained reaching a maximum of 29 per cent on the twenty-fourth day (Table II). A third bone marrow examination showed a great increase in the percentage of erythroid elements predominantly normoblastic in morphology.

The infant began to eat normally, gained in weight and strength. Antianemic therapy was discontinued. He was discharged home thirty-two days after the beginning of treatment. The total serum proteins had risen to 6.9 Gm. per 100 c.c. with albumin 4.3 Gm. and globulin 2.6 Gm. In the stained blood films some of the red cells remained macrocytic. The bone marrow showed normoblastic cell development.

On a check-up examination six weeks later the infant was perfectly well to all outward appearances. He had continued to eat well and had gained 4 pounds in weight. The blood values were within range of normal (Table II). The bone marrow showed no abnormalities.

DISCUSSION

Megaloblastic anemia in infants is being recognized more frequently with the wider employment of detailed hematologic studies, especially bone marrow

TABLE II. HEMATOLOGIC FINDINGS IN CASE 2, W. J. P., C-44538

DATE 1948	Hb. (GM. PER 100 C.C.)	RBC (MILLIONS PER CU.MM.)	HEMATOCRIT	RETICULOCYTE (PER CENT)	DAY OF THERAPY	DIFFERENTIAL WBC AND THERAPY
9/24	10.9	3.1	29.5	1.3		Segmented polymorphonuclears 30, stabs 7, metamyelocytes 1, lymphocytes 58, monocytes 3, eosinophile 1.
9/25	*Tibial Marrow:* Segmented polymorphonuclears 4.5, stabs 33, metamyelocytes 23.5, myelocytes 12, myeloblasts 0.5, lymphocytes 4.5, eosinophiles 5, acidophilic megaloblasts 5.5, basophilic megaloblasts 9, promegaloblasts 2.5. Leucocyte: nucleated red cell ratio = 4.9:1					
9/27	10.2	3.1	28	1.1	0	Vitamin B_{12}, 0.002 mg.
9/28				1.2	1	
9/29				0.4	2	
9/30				1.9	3	
10/1	9.5	2.9	26	2.2	4	
10/2				0.9	5	
10/4	9.2	2.8	25.2	3.2	7	Vitamin B_{12}, 0.005 mg.
10/5				3.3	8	
10/6				31.7	9	
10/7				10.2	10	
10/8	8.9	2.8	26.8	5.9	11	
	Tibial Marrow: Megaloblastic erythroid development. Leucocyte: nucleated red cell ratio = 2.8:1					
10/9				3.1	12	Vitamin B_{12}, 0.002 mg.
10/10					13	Vitamin B_{12}, 0.002 mg.
10/11	7.7	2.5	22	5.0	14	Vitamin B_{12}, 0.002 mg.
10/12				6.2	15	Vitamin B_{12}, 0.002 mg.
10/13				6.6	16	Vitamin B_{12}, 0.002 mg.
10/14				5.3	17	Vitamin B_{12}, 0.002 mg.
10/15	7.7	2.4	21.2	4.7	18	
10/16				10.2	19	
10/18				18.7	21	Vitamin B_{12}, 0.002 mg.
10/19	8	2.5	24.1	19.4	22	Vitamin B_{12}, 0.002 mg.
10/20				24.6	23	Vitamin B_{12}, 0.002 mg.
10/21				29	24	Vitamin B_{12}, 0.002 mg.
	Tibial Marrow: Leucocyte: nucleated red cell ratio = 1.2:1					
10/22	10	3		16.7	25	Vitamin B_{12}, 0.002 mg.
10/23				14.5	26	Vitamin B_{12}, 0.002 mg.
10/24					27	Vitamin B_{12}, 0.002 mg.
10/25				13.6	28	Vitamin B_{12}, 0.002 mg.
10/26	10.9	3.3	32.5	10.9	29	Vitamin B_{12}, 0.002 mg.
10/27				12.8	30	Vitamin B_{12}, 0.002 mg.
10/28				11.2	31	Vitamin B_{12}, 0.002 mg.
10/29	12	3.5	33	8.8	32	Vitamin B_{12}, 0.002 mg.
	Tibial Marrow: Normoblastic erythropoiesis. Leucocyte: nucleated red cell ratio = 2.8:1					
12/7	12	3.9	37	2.8	71	
	Tibial Marrow: Leucocyte: nucleated red cell ratio = 3.8:1					

examinations.[12] Anemias developing in infancy during or following infection, or in association with feeding difficulties, are particularly suggestive of this entity. Our Case 1, apparently the first Negro infant reported to have this type of anemia,[9, 12] indicates that there is no real racial immunity. Some infants probably recover more or less spontaneously with treatment of infection, blood transfusions, general nutritional therapy, etc.[2, 4] Opportunities for early and specific treatment should not be overlooked, however, since eight of the twenty-five seriously ill infants reported by Zuelzer and Ogden[12] died of the anemia or its complications.

The megaloblastic anemia of infants is more comparable to nutritional macrocytic anemia in adults and the macrocytic anemia of sprue or idiopathic steatorrhea than to pernicious anemia. Only in the latter is histamine refractory gastric achlorhydria a constant feature. Pernicious anemia is distinguished, also, by an anemia showing hemolytic features, the frequent occurrence of serious neurologic manifestations, and the necessity for permanent antianemic therapy.

The quantitative response of the anemia to liver extract or pteroylglutamic acid has been variable. The reticulocyte rise is often slight and regeneration of red cells and hemoglobin slow. This is probably due to the gravity of the associated complications, particularly infection. Several weeks or repeated courses of therapy may be necessary before the anemia is corrected.[3] In our Case 1, an experiment in minimal dosage of vitamin B_{12}, there was a prompt and dramatic hemopoietic response. In Case 2 more prolonged therapy was required. A quantitative regeneration of the entire erythroid series apparently occurred. The variable response of the anemia makes comparison of the relative effectiveness of different therapeutic compounds difficult. That vitamin B_{12} is effective at all is of interest, for early reports indicate that minute amounts of the substance have the therapeutic activity of refined liver extract.[10, 11] In pernicious anemia vitamin B_{12} has a nutritional value lacking in pteroylglutamic acid.[8] There is no definite evidence to indicate, however, that pteroylglutamic acid is not a completely effective compound in the treatment of megaloblastic anemia of infancy.

SUMMARY

Two infants, one a Negro, with megaloblastic anemia were treated with vitamin B_{12}. Both responded favorably, one to a single injection of 0.002 mg. of the compound.

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GLYCOGEN DISEASE OF THE LIVER

With Report of a Case

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THOUGH glycogen disease of the liver was first described by Snapper and Van Creveld,[21] Von Gierke[23] reported two cases which came to autopsy, and his name has been given to this condition. The whole subject has been reviewed by Van Creveld.[22] The disease is characterized by the accumulation of excessive quantities of glycogen in the liver, kidneys, skeletal muscles, or heart. Deposits have also been found in the brain, and the blood glycogen has been found to be raised in some cases. The liver is most often affected, sometimes the kidneys also, as in Von Gierke's original two cases, and the skeletal muscles, but despite the enormous accumulation of glycogen no gross disturbance in the function of these organs results, except in the case of the heart, whose involvement alone has been described with heart failure in infancy. Mason and Andersen[17] would restrict the name of Von Gierke's disease to those cases in which the liver is predominantly involved; they stated that up to that date only thirty-four cases in which they considered the diagnosis to have been proved had been described. Crawford,[6] adding three cases of his own, mentions eight others. Since then, cases have been described by Schneider[18] (two cases). Abramson and Kurtz[1] (four cases), Bridge and Holt[3] (two cases), and Chieffi and Nassi[4] (three cases). Manter and Bowman[16] state that no cases were seen in Rhode Island Hospital between 1934 and 1942 in over 5,000 admissions. The condition, therefore, is a rare one, and partly on this account and partly because of some improvement with treatment, the following case is described.

CASE REPORT

The patient, a male, was first seen at the Princess Louise Hospital for Children, London, on Nov. 1, 1938, at the age of 14 months, suffering from stomatitis. On routine examination hepatomegaly was discovered and he was admitted for investigation. The mother had been well throughout the pregnancy; the child, her first, was born at full term by normal delivery and weighed 7½ pounds at birth. He was breast fed for one year and had had no illnesses except for rubella. Milestones were normal. The mother had not considered his abdomen to be of excessive size. Mother and father were both alive and well and not related. No family illness was admitted.

Examination.—The child weighed 24 pounds. Ten teeth were present. Apart from stomatitis, the only abnormality noted was in the abdomen, which was distended and showed prominent upper abdominal veins. The liver was enlarged down to the umbilicus. The spleen was not palpable.

A glucose tolerance test (Fig. 2, Table I) was done, following the ingestion of 25 Gm. glucose. The Wassermann reaction was negative, icteric index

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3, fecal fats 21.2 per cent with 81 per cent split, and the blood count was hemoglobin 70 per cent, red blood cells 3,860,000, white blood cells 5,500, and 72 per cent polymorphonuclears. There is no record of the urine having been examined for ketone bodies and neither an adrenaline response test nor an estimation of blood cholesterol was made.

The boy was kept in the hospital until the end of January, 1939. After the stomatitis cleared up he remained well, but the abdominal distention increased, and on discharge the liver was palpable 1 inch below the umbilicus and the abdominal circumference at the umbilicus was 22½ inches.

Fig. 1.—Patient with normal boy of same age.

He was seen in the outpatient department at intervals and remained well except for frequent coughs and colds. In March, 1939, he was described as flabby and he was said to tire easily. His weight was then 27 pounds and the abdominal circumference 27 inches. During this month he had a few episodes

of vomiting which were relieved by giving glucose. He was not seen for seven years after April, 1940, when neither the weight nor the size of the liver were recorded, but the abdominal distention was less and the circumference at the umbilicus was 25 inches.

He was next seen on June 11, 1947, at the age of 9 years, having been sent by his school doctor because of obesity. He had remained well since his last attendance and his school record was satisfactory. He was stated to be a big eater, especially of starchy foods.

TABLE I. ORAL GLUCOSE TOLERANCE TESTS (BLOOD SUGAR MG. PER 100 C.C.)

DATE	FASTING	½ HOUR	1 HOUR	1½ HOURS	2 HOURS
1/24/39	89	89	125	107	107
6/16/47	57	156	113	96	93
6/28/47	63	106	111	161	114

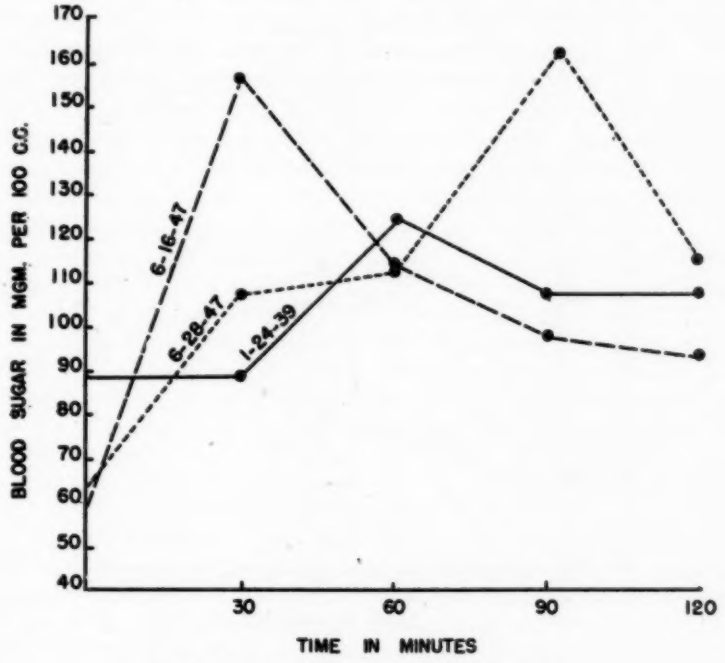

Fig. 2.—Blood sugar curves after oral glucose.

The family now included two brothers aged 3 years and 2 years. The liver of the younger was palpable one fingerbreadth below the costal margin in the nipple line, but the mother refused to allow further investigations to be carried out. She is a large, obese woman, while her husband is slightly below normal size. He maintains that in his youth his condition was similar to that of his eldest son and that he remained obese until the age of 23 years. Photographs of him at the age of 11 years bear out this, but it has not been possible to obtain any medical evidence of his past history. No clinical abnormality can now be detected and there is no ketonuria.

The patient was admitted to the hospital for investigation on June 11, 1947. His weight was 66 pounds (average for his age is 67 pounds) and height 47 inches (average, 52 inches). He was slow and deliberate in movement and in his mental processes, but his intelligence was normal for his age. The abdomen was protuberant and the circumference 32½ inches at the umbilicus. The liver was enlarged down to the umbilicus and was firm and smooth. The left kidney was palpable but not the spleen. The external genitals appeared small, but this could be largely due to the obesity.

The urine at all times of the day contained ketone bodies, detected by Rothera's but never by Gerhardt's test. The results of glucose tolerance tests done on June 16 and June 28, after 50 Gm. glucose, are shown in Fig. 2 and Table I, and of adrenaline response tests on June 17 and June 29 in Fig. 3 and Table II. The blood cholesterol was 260 mg. per cent. Wassermann reaction and Kahn tests were negative. Full blood count was normal and x-rays of skull, chest, and long bones were normal. A straight x-ray of the abdomen showed the kidneys to be slightly enlarged.

TABLE II. ADRENALINE RESPONSE TESTS (BLOOD SUGAR MG. PER 100 C.C.)

DATE	FASTING	15 MINUTES	30 MINUTES	MAX. RISE
6/17/47	57	60	56	3
6/29/47	58	64	54	6
1/21/48	38	47	59	21

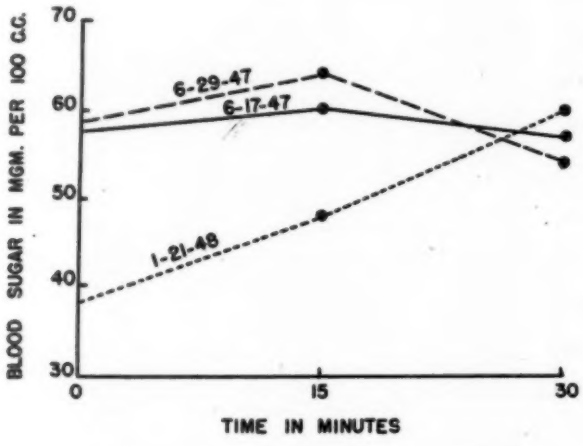

Fig. 3.—Adrenaline response tests (5 minims adren: HCl 1/1000, S.C.I.).

Treatment with Chonex tablets, one three times a day, was started on June 21, 1947, and the dose was increased to two tablets three times a day on June 25, 1947. (Each tablet contained 5 grains of dehydrocholic acid.)

Rothera's test, which was faintly positive on June 25, was negative in all specimens the next day and remained so until he was discharged on July 1, to continue taking two Chonex tablets three times a day. His weight was then 69 pounds.

He was seen in the outpatient department at intervals. There was no ketonuria in an early morning specimen in mid-July. However, when he next at-

tended at the end of October, ketone bodies were again detected in the urine but he had had no tablets for two and one-half months as he had not attended for a fresh supply. His weight was then 75 pounds. Chonex tablets were again given, and in December the mother thought he was more active. At the end of January, 1948, his weight was 75 pounds. The liver was still palpable at the umbilicus, but the abdominal circumference had decreased to 29¾ inches. Rothera's test was positive, but the specimen tested was not passed until 11 A.M., and he had had no food that day. An adrenaline response test was performed (see Fig. 3).

Discussion.—There seems no doubt that this patient is suffering from glycogen disease of the liver, although the final proof would depend on a liver biopsy and this the parents refused.

Mason and Anderson[17] consider the essential features to be marked hepatomegaly without splenomegaly from early life, a tendency to ketosis, no hyperglycemic response to the injection of adrenaline, and a delayed fall in the blood sugar curve. Van Creveld[22] pays great attention to the adrenaline response, but considers it probably superfluous if ketonuria is already present. All Mason and Andersen's criteria are fulfilled by this case. The only alternative diagnosis would appear to be hypertrophic steatosis of the liver,[8] in which there is a gross accumulation of fat in the liver without evidence of any infection to account for it. The clinical features and prognosis of this condition and of glycogen disease of the liver are similar, and Debré[7] classifies them together as *hepatomegalie polycorique:* in his opinion differentiation is only possible by liver biopsy, although he agrees with Van Creveld[22] that hypercholesterolemia and ketonuria are not features of hypertrophic steatosis. Ketonuria was not a feature of the case of hypertrophic steatosis reported by Kraymer, Grayzel, and Solomon[13] and Van Creveld considered that the presence or absence of ketonuria differentiated the two conditions. Debré is unwilling to accept this as an absolute point of distinction, and considers that hypertrophic steatosis should be regarded as closely allied to glycogen disease, following it or preceding it, but most often combined with it. Personal observation has shown that certain patients with fatty livers, as well as those with livers filled with excess glycogen, show a low fasting blood sugar level, abnormal glucose tolerance curves, and lack of adrenaline response: it is also true that excess fat as well as glycogen may be found at autopsy in the livers of patients dying of glycogen disease, an observation first made in Von Gierke's original two cases and subsequently confirmed by others. As a general rule, glycogen and fat are mutually exclusive in the liver and it would appear desirable to separate the two conditions in which an excess of either is present. The evidence points to such a separation being possible by the presence of hypercholesterolemia and ketonuria in glycogen disease of the liver and not in hypertrophic steatosis.

Apart from infantilism which tends to be more obvious when the condition has been present for a number of years, glycogen disease of the liver is usually symptomless, but attacks of vomiting and a preference for carbohydrates (as in this boy) have been recorded previously. Obesity has been present in a number of cases.

In 70 per cent of normal children the fasting blood sugar level lies between 75 and 100 mg. per cent.[5] In glycogen disease values below these levels are obtained and in the glucose tolerance test the essential feature is the delayed return to the fasting level. The curve may be high or flat and a diphasic type has been frequently noted.

Van Creveld[23] states that no treatment is effective. He did, however, abolish ketonuria in a case of glycogen disease by giving choline. The rationale of this treatment is that choline is a lipotrope and prevents deposition of fat in the liver which is the only source of production of ketone bodies: these are derived from the oxidation of fats. Deuel and associates[9] found that choline given to fasting rats after a high fat diet reduced the amount of ketone bodies in the urine as compared with controls, and MacKay and Barnes[15] obtained a similar result in fasting rats in whom ketonuria had been produced by injection of anterior pituitary extracts.

Bile salts were given to this patient because of the report by Linneweh[14] that during the administration of a bile-acid-lecithin compound over a period of three months to a patient suffering from glycogen disease, the liver had decreased in size: he had previously observed the disappearance of glycogen from frogs' livers in winter in an irrigation experiment with bile salts. Linneweh considered that these results were obtained by the action of bile salts in potentiating the activity of "liver diastase" by diminishing its fixation to the intracellular boundaries. Seckel[19] produced glycogenolysis in rats' livers in vitro by perfusing them with bile salts, and he postulated that the latter acted by virtue of their surface activity: he quotes Forsgren's observation that in adults and in animals a high bile acid secretion is associated with a low level of hepatic glycogen and vice versa. Although the steps in the breakdown of glycogen to glucose have now been worked out, it is not possible to explain how bile salts influence this reaction. Linneweh's explanation is at the least an oversimplification, since it is now believed that not one but a number of enzymes are involved in glycogenolysis.

Seckel,[19] Holt and McIntosh,[12] and Debré[7] refer to the treatment of glycogen disease by bile salts, but Linneweh alone appears to have actually used this treatment. It is of interest that temporary improvement has been recorded in two cases of glycogen disease during attacks of infective hepatitis. Anderson[2] noted a decrease in the ketonuria despite the fever, and Sundal (quoted by Holt and McIntosh) a diminution in the size of the liver.

With the administration of bile salts in this case there was a rapid disappearance of ketonuria, a decrease in the abdominal circumference of 2¾ inches over seven months and no further gain in weight over a period of four months. It would be unwise to draw any conclusion as to the efficacy of treatment from the last adrenaline response test since, although the rise in the blood sugar level is more than that obtained previously, the results of the test are still not normal, as there should be a rise of at least 30 mg. per 100 c.c. in thirty minutes.[10]

Unfortunately it has not been possible to carry out further tests since the boy has not attended again, and repeated requests to the parents have been

fruitless. Their attitude is understandable, though regrettable, since they point out that the boy is in no way ill and the father believes firmly that the boy will recover spontaneously in the same way as he thinks he did himself.

No case of direct inheritance has been recorded, but familial cases have been described and Ellis and Payne[10] postulated the inheritance as a Mendelian recessive character. The history of the father of this boy is most interesting and raises much speculation.

It has been supposed that the prognosis is not good as there is an increased susceptibility to infections, but neither Van Creveld nor Debré is in agreement with this. Certainly the prognosis would seem to be excellent in this boy. There are a number of reports in the literature of spontaneous cure at or about puberty. In Worster-Drought's case, in which puberty was delayed till 17 years of age, the liver which had extended 3 inches below the costal margin at the age of 10 years was no longer palpable at the age of 22, though acetone was present in the breath.[24] In Van Creveld's first case, in the boy's middle teens the fasting blood sugar level rose, the ketosis lessened and the liver became smaller. Von Gierke (quoted by Van Creveld) described a post-mortem examination on a girl of 15 years suffering from the disease, in which, although most of the liver presented the typical appearance, there were scattered areas of normal liver tissue. This was interpreted as possibly signifying commencing spontaneous recovery. Debré[7] records spontaneous cure at puberty in a patient of his own: he considers that patients tend to improve at puberty and become perfectly normal, but that this is not an invariable happening since some retain the stigmata of infantilism and enlargement of the liver. He states that even after the liver has returned to normal size the abnormal biochemical tests persist from some time, especially the presence of acetone in the breath and in the urine.

Apart from Worster-Drought's patient, all those whose cases are recorded in the literature are under 18 years of age and the majority are under 12 years old. This would suggest that spontaneous cure does occur since it is hard to believe that all died before adult life was reached.

The conception that spontaneous cure occurs at puberty is consistent with the hypothesis first advanced by Hertz[11] that glycogen disease is due to hypofunction of the anterior pituitary, since there is increased activity of the pituitary at puberty.[20] It is, however, necessary to postulate hypofunction of the pituitary-hypothalamic mechanism as does Debré,[7] since obesity of pure pituitary origin is due to increased activity of the anterior pituitary but may occur with hypothalamic lesions.[20] It is true that retardation of skeletal and sexual development, obesity, and increased sensitivity to the injection of insulin are common to glycogen disease and to hypofunction of the pituitary-hypothalamic mechanism, but it has been argued that these features in glycogen disease may be equally well explained by the disturbance of carbohydrate metabolism, that no pathologic changes in the pituitary have been found at autopsy (though it is agreed that there may be disturbance of function without demonstrable pathologic change), and that glycogen disease has not been reproduced in animals by

destruction of the anterior pituitary or hypothalamus; in fact, in experimental animals extirpation of the pituitary causes great diminution of the glycogen stores. Debré,[7] however, has brought forward further evidence: he quotes Képinov, who found that in the frog the glycogenolytic action of adrenaline was destroyed by removal of the pituitary but restored by the simultaneous injection of adrenaline and pituitary extract, and who postulated that glycogenolysis in the liver was dependent on the fixation of adrenaline on the hepatic cells by a pituitary glycogenotropic hormone. Debré also quotes work by Lamotte-Barrillion, who perfused the livers of hypophysectomized frogs with adrenaline and serum and obtained glycogenolysis when using serum from normal persons but not when using serum from patients suffering from glycogen disease; it was, therefore, concluded that in the latter a glycogenotropic hormone was absent from the serum. This work requires confirmation and, although it brings forward more cogent evidence in favor of a pituitary-hypothalamic disturbance, no improvement has been obtained in cases of glycogen disease by the injection of pituitary extracts.[7] The evidence, therefore, is, as yet, inconclusive.

SUMMARY

1. A case of glycogen disease of the liver is described.

2. Treatment with bile salts produced disappearance of ketonuria and decrease in the girth of the abdomen.

3. The diagnosis and prognosis are discussed.

4. The hypothesis that a pituitary-hypothalamic hypofunction is the cause of glycogen disease has recently received fresh support.

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THE INFLUENCE OF ACUTE INFECTION UPON THE COURSE OF ALLERGY IN CHILDREN

Some Clinical Observations

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ANY consideration of the role of infection in the allergic child immediately raises the problem of bacterial sensitivity. Current observations in immunology demonstrate that either bacteria or bacterial products may produce tissue hypersensitivity with ensuing tissue changes which in most instances differ qualitatively from the pathology associated with nonbacterial hypersensitivity. In bacterial hypersensitivity fixed tissue changes are usually observed which are in distinct contrast to the reversible lesions resulting from edema seen with nonbacterial hypersensitivity. The identity of the mechanisms concerned with the two types of hypersensitivity has not been demonstrated. It is probable that bacterial sensitivity operates through a system entirely independent of the factors concerned with nonbacterial hypersensitivity, although it is likely that a single mechanism could operate in both instances with qualitative and quantitative variations in the tissue response, depending upon the nature of the antigen activating the system.

In addition to the ability of infection to produce a type of tissue hypersensitivity, clinical observations indicate that infection may play a role in the phenomena of allergy by influencing the clinical course of existing allergy. The purpose of this communication is to report on some clinical observations which demonstrate that a relationship does exist between infection and allergy in the child.

An allergic child with an acute infection presents a distinct pattern for his allergy. The pattern observed is one of two types, depending upon the nature of the infection. The first pattern is observed in association with pertussis, the infectious diseases—measles, chickenpox, and mumps, and the epidemic virus diseases. In these diseases the symptoms of allergy are aggravated during the period of invasion or the prodromal stage. During this stage, a child suffering with allergic rhinitis will have more severe nasal symptoms; the asthmatic child will have more severe asthma or allergic bronchitis; and the eczematous child will have an aggravation of his rash. As these acute infectious diseases approach their fastigium, there is a decrease in the severity of the symptoms of allergy. At the peak of the illness the child's allergy is at a lower level than he ordinarily experiences. Clinically he may be entirely free of the signs and symptoms of allergy. This stage corresponds with the paroxysmal phase of pertussis and the eruptive period of the infectious diseases. The child who had nasal symptoms of allergy will be entirely free; the

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asthmatic child will offer no pulmonary findings; the eczematous child will have a clear skin. With convalescence there is a recrudescence of the allergy, that is, with convalescence the signs and symptoms of allergy not only recur, but recur with greater severity and greater intensity than before the onset of the acute infectious disease. As will be observed in Fig. 1, which schematically illustrates allergy influenced by the named infections, a new base line has been established for the allergy. Prior to the infection the symptoms of allergy, though present, may be extremely mild and require little if

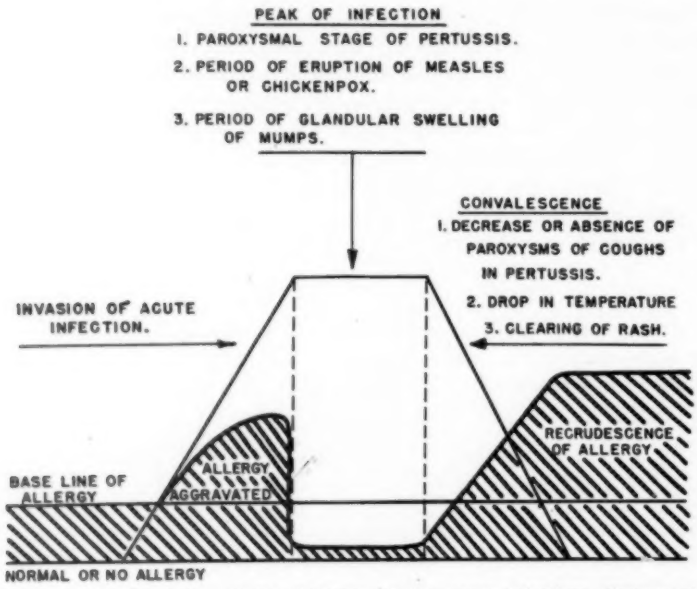
PEAK OF INFECTION
1. PAROXYSMAL STAGE OF PERTUSSIS.
2. PERIOD OF ERUPTION OF MEASLES OR CHICKENPOX.
3. PERIOD OF GLANDULAR SWELLING OF MUMPS.
CONVALESCENCE
1. DECREASE OR ABSENCE OF PAROXYSMS OF COUGHS IN PERTUSSIS.
2. DROP IN TEMPERATURE
3. CLEARING OF RASH.
INVASION OF ACUTE INFECTION.
RECRUDESCENCE OF ALLERGY
ALLERGY AGGRAVATED
BASE LINE OF ALLERGY
NORMAL OR NO ALLERGY

Fig. 1.—Schematic presentation of the influence of the acute infectious diseases upon the clinical course of allergy.

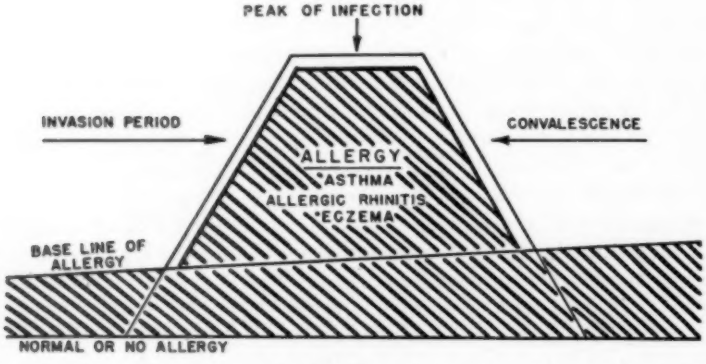

Fig. 2.—Schematic presentation of the influence of an acute upper respiratory infection (bacterial) upon the clinical course of allergy.

any medical management. Following the acute infectious process, the allergy becomes aggravated to such a degree that the child may experience his first attack of asthma. A mild eczema may become a severe eczema, or a mild rhinitis may present constantly annoying symptoms.

The second pattern is observed most commonly in association with acute infections of the upper respiratory tract, that is, rhinopharyngitis, acute tonsillitis with or without adenitis, adenoiditis, sinusitis, acute otitis, or any combination of involvement of the upper respiratory tract. In these infections there is no apparent change in the allergy during the period of invasion but at the height of the infection there is an aggravation of the allergy. Concomitant with the peak of the acute infectious process there is an aggravation of nasal symptoms or of the pulmonary symptoms which may be manifested by acute asthma or allergic bronchitis, or the rash of eczema may become more severe and itching is frequently more intense.

DISCUSSION

An analysis of some of the observations and attitudes on infection in the allergic child expressed in the literature in comparison with the two patterns presented raises some interesting points for discussion.

The exacerbation of allergy by measles is mentioned by Peshkin[1] who observed that asthma frequently recurred or was aggravated during the incubation period of measles, but with the appearance of fever the asthma cleared in the majority of these patients. No other such observation has been noted in the literature. The lack of further reports on the exacerbation of allergy during the invasion of an acute infectious process perhaps can be explained by its failure to occur as a constant finding. As the degree of aggravation of the allergy during this phase of the acute infectious process is usually not as severe as that seen following the disease, the clinician may overlook this observation unless he is alerted to the over-all pattern produced by an acute infectious process in the allergic child. In some cases, during the invasion of a contagious disease, the symptoms of allergy may return with greater violence and fail to respond to the usual medical management. With the establishment of the fastigium of the disease, the symptoms of allergy disappear completely. This observation is not peculiar to children. In a female, aged 37 years, whose asthma of many years' standing was controlled with a pollen antigen, the asthma suddenly recurred and persisted for ten days, when with equal suddenness the asthma cleared. The cough present since the onset of the asthma increased in severity and became paroxysmal. During this stage the chest was clear. The blood count revealed 12,000 leucocytes with 44 per cent polymorphonuclear leucocytes, 54 per cent lymphocytes, and 2 per cent monocytes. The diagnosis was pertussis. An almost similar history was experienced in an adult female, aged 28 years, whose asthma was under control. For one week prior to the establishment of clinical signs of epidemic parotitis the patient experienced a severe attack of asthma. Concomitant with the swelling of the parotid the asthma cleared.

Improvement of the signs and symptoms of allergy at the peak of an acute infectious process is also reported in the literature. Very early in the history of clinical allergy, Pirquet observed that a positive tuberculin may become negative during measles. In a discussion of desensitization, Rich[2] also points out "that the cutaneous reactivity to tuberculin often diminished markedly during the early stage of the exanthem of measles, to return again after a week or two. A similar diminution in reactivity has been observed during other acute infections." The clearing of eczema with measles is a common clinical observation. We have already noted Peshkin's[1] observations that asthma cleared with the appearance of fever of measles. Very little note has been made in the pediatric literature of the very important observation that a positive tuberculin becomes negative during the paroxysmal stage of pertussis, which was reported by both Galli[3] and Pospischill[3a] at about the same period that Pirquet reported on the tuberculin response during measles. The writer has questioned many clinicians, both pediatricians and allergists, and none can recall the occurrence of asthma during the paroxysmal stage of pertussis. Rackemann[4] states that when Allergy is well established, the effect of an intercurrent infection will depend upon its severity. An acute infection of relative severity, he states, may alleviate the allergy temporarily. The allergic child who gets measles will lose his eczema or asthma at the time of the intercurrent disease. Rackemann's opinion differs from our experience. The influence upon the allergic state is not related to the severity of the infection but the nature of the infection. The acute infectious diseases, measles, mumps, chickenpox, and pertussis, will show an improvement in the allergic state at the peak of the infectious process without relation to the severity of the infection.

In Case 1, reported later, illustrating eczema influenced by measles, the child suffered a modified measles following the administration of immune globulin. In Case 2 illustrating the influence of measles on the course of asthma, the child suffered with a severe reaction to his measles, but during the period of intense eruption his chest was clear and there were no symptoms of asthma.

In Cases 7 and 8 illustrating eczema influenced by chickenpox, one child suffered a severe infection with chickenpox while the other child had only a mild infection. These cases serve to illustrate that severity of the infection is not the influencing factor. With the acute infectious processes, regardless of the intensity of the infection, allergy will improve, while in the upper respiratory infections, allergy is aggravated at the peak of the infection. Here again, severity of the infection is not the determining factor. This would seem to indicate that the nature of the infection is the influencing factor rather than degree of infection.

The contention that fever is the determining factor when allergy improves during the course of an acute infectious process can be disclaimed by the same argument. During the course of the diseases mentioned in association with pattern 1, clinical allergy will improve without regard to the degree

of fever while in severe upper respiratory infections accompanied by high temperatures, even up to 104° or 105° F., the allergy may be aggravated. Fever may be a manifestation of an allergic response as is observed in serum sickness, the classical example of the acute allergic reaction or as has been more recently observed in penicillin reactions.

There is a difference in the immunologic responses in the two groups of infections as is evidenced by the fact that the first group calls forth a leucopenia or lymphocytosis in the blood picture, while the second group evokes a polymorphonuclear leucocytic response. The first group usually confers an immunity after a single infection while the second group confers no immunity. This immunologic difference between the two groups of infections is consistent with the observations reported by Bunting[5] and also Ehrich and Harris.[6] These investigators state, "That the polymorphonuclear leukocyte does not play a part in antitoxic immunity seems to be indicated by a series of clinical observations which have been summarized in a general law of pathology to the effect that no disease which runs its course with a neutrophile leucocytosis is followed by lasting immunity. A high lymphocyte-monocyte ratio suggests resistance."

The aggravation of the allergic state by an infectious process as evidenced by the onset of the first attack of asthma is well recorded in the literature. Practically every modern text on either pediatrics or allergy cites the infectious processes as precursors in the onset of asthma and emphasizes the frequency of pertussis as an exciting agent.

In a study on the incidence and significance of various diseases and infections in asthma in children, Peshkin[1] pointed out the frequency of association of pertussis and measles with the onset of asthma. Walzer[7] states that among the common contagious diseases of childhood involving the respiratory tract, pertussis out-strips all others as an etiologic factor in asthma. Walzer also reports that a number of nonsensitive middle-aged asthmatics dated the onset of their asthma to the influenza epidemics of the last decade. Bray[8] observes that at least one out of each three cases of asthma that one sees will assign the onset to some infectious disease, and whooping cough and pneumonia are by far the commonest. Dienes[9] states that no doubt at times certain changes occur which predispose to sensitiveness. During infections such as whooping cough, that part of the system which makes antibodies is much more irritable. He believes that sensitiveness frequently follows infections. Rackemann[4] reported a similar attitude when he states that an acute infection irritates that part of the system which makes antibodies. Asthma may often begin after whooping cough, measles, or other acute infections. In reporting on prophylaxis in allergy, Ratner[10] also emphasizes the importance of measles and pertussis in antedating asthma. In a discussion on the etiology of asthma, Tuft[11] indicates the frequency of a history of pneumonia, influenza, or pertussis prior to the onset of the initial asthmatic attack. In his text *Allergy in Theory and Practice,* Cooke[12] expresses the opinion that, "A clinical history of an acute infection especially measles, pneumonia, influenza,

or bronchitis as the precursor of an allergy is obtained too frequently to be overlooked or to be rejected as of no moment. Infection as provocative of an allergy but not specifically and causally related to that allergy is an idea that must be investigated further.'' Cooke's statement is very pertinent. The infectious processes may not only play a definite role in the causation of clinical allergy but as illustrated by pattern 1 may have a distinct influence upon the course of the allergy. The occurrence of clinical allergy following an acute infectious disease is only one phase of the interplay between allergy and the acute infectious processes. The influence of the infectious processes upon the course of allergy raises many problems for investigation. Why is the alteration in the pattern of the allergic state by the infectious processes not a constant manifestation? In some cases the aggravation of the allergic state during the period of invasion may be observed with no recrudescence during or following convalescence. On the other hand, the exacerbation of clinical allergy following an acute infectious process may occur without any apparent influence upon the allergy during the phase of invasion. That this clinical observation is not uncommon is implied by the literature which frequently mentions the acute infectious processes as precursors of clinical allergy. The only constant observation is the improvement of the allergic state during the fastigium of the infectious diseases. Correlation of these clinical observations with immunologic studies would no doubt reveal the answers to some of these clinical phenomena.

The aggravation of the allergic state by the acute respiratory infections is generally accepted in pediatric practice and is cited frequently in the literature by observers reporting on infection in allergy. The allergy is most severe at the peak of acute infection. The allergic symptoms in association with this type of infection do not respond to the usual medical management for allergy. The best response is observed following the use of antibiotics, either sulfonamides or penicillin. As the infection subsides, the symptoms of allergy improve without any specific therapy directed toward the allergy.

CASE REPORTS

CASE 1.—M. S., a 14-month-old male child, was first seen on Jan. 20, 1948, with a complaint of generalized eczema. The eruption first appeared on the malar eminences a few days after birth. The rash became progressively worse involving both cheeks and the bends of the arms and legs, and soon after, the entire body was involved. The eruption was perennial showing no period of remission or improvement in any season of the year.

On physical examination the child had a temperature of 101° F. rectally. The development was good. The anterior fontanel was closed but the nutrition was very poor. All the symptoms were negative except the findings of the nose and skin. The nasal mucosa was pale and boggy and the turbinates were markedly edematous. There was a thin mucoid discharge on the floor of the nose. The skin of the entire body showed some involvement by an erythematous, dry, scaly eruption with a marked degree of secondary infection, folliculitis, and scratch marks. Over the scalp there was considerable dry exudate; itching was intense. All the superficial lymph nodes (cervical,

axillary, inguinal) were enlarged and doughy. A blood count at this time showed hemoglobin 69 per cent, erythrocytes 4,360,000, leucocytes 25,000 with 60 per cent neutrophiles of which 52 were segmented, 29 per cent lymphocytes, 9 per cent monocytes, and 2 per cent eosinophiles.

Because of the marked infection, testing was delayed and treatment was directed against the secondary infection. Soaks in a solution of magnesium sulfate were instituted and 100,000 units of penicillin were administered every eight hours. The secondary infection subsided and the lymph nodes receded. The general condition of the skin showed a marked improvement. The torso was almost entirely clear and lesions of a nonexudative eczema were limited to the extremities particularly the flexural surfaces. The child was tested and was found extremely reactive to all the important environmental factors. In view of these findings the child was placed on a full diet with strict environmental control and treatment with an epidermal antigen. By March 12, 1948, the child's skin was completely clear, the lymph nodes had receded, nutrition had improved, and the child's well-being was excellent.

On March 24, 1948, the child was exposed to measles. One week later, March 31, he received human immune globulin. April 1, the child again showed a few small eczematous lesions in the flexural folds of the arms and legs. On April 4, the child experienced his first attack of asthma which responded to adrenalin. On the following day, his temperature rose to 101° F. rectally. On April 7, his temperature rose to 103.5° F. rectally and the exanthem of measles appeared. With the appearance of the rash the eczema cleared. There were no chest findings. On April 9, the child was fever-free. The evening of the same day the rash of eczema recurred on the face, arms, back of the neck, and the shoulders. When seen on June 17, the skin was entirely clear except for a few small excoriated lesions in the bends of the forearms. On August 12, the skin was entirely clear.

Note: This case illustrates the influence of measles in the course of allergy. The child experienced his first asthma with invasion of his measles. The eczema recurred at the same phase of the infection, cleared with the rash, and then recurred with convalescence. The influence on the allergy occurred although the child had a very mild case of measles.

CASE 2.—L. J., a 4-year-old child, was first seen on Aug. 4, 1947, with a complaint of eczema and asthma. The eczema appeared shortly after birth, involving the flexural surfaces of the arms and legs and the buttocks and had never cleared since its first appearance. There were no seasonal variations.

In April, 1945, the child had his first attack of asthma. The asthmatic attacks were preceded by itching of the nose, sneezing, and a watery discharge, followed by coughing and wheezing of two days' duration. The asthma was worse in the summer, but the cough was a perennial symptom.

On physical examination, the nasal mucosa was very pale and boggy, and the turbinates were edematous. There was a clear mucoid discharge on the floor of the nose. The tonsils were moderately enlarged and pale. There was no lymphoid studding of the postpharyngeal wall. The uvula was edematous and there was considerable postnasal drip. The cervical nodes were not enlarged. The chest was symmetrical. Movements were free and equal. On auscultation the breath sounds were harsh in character with prolongation of the expiratory phase. There were numerous coarse rhonchi intermingled with sonorous and sibilant râles. The heart was negative. The skin showed a dry, scaly, erythematous eruption with scratch marks limited to the flexural surfaces of the extremities. A nasal smear was positive for eosinophiles and pus

cells. On intradermal testing, the child reacted strongly to many important foods, the common environmental factors, and all the important pollens of Southern California. The child was managed by a strict environmental control, omission of the important food factors, and rotation of the diet combined with treatment with a pollen antigen which he started on Nov. 5, 1947. By Feb. 26, 1948, the child showed a definite improvement. The eczema cleared and he suffered only an occasional mild asthmatic attack. Between attacks the chest was clear. On June 23, 1948, the child was exposed to measles. On July 1, examination of the chest revealed a few rhonchi and sibilant râles. He was given 2 c.c. of immune globulin. On July 7, the child had an attack of severe asthma which responded only temporarily to 0.4 c.c. of adrenalin. Koplik spots were observed on the buccal mucosa. On July 9, the child's temperature rose to 104° F. rectally. The exanthem of measles appeared. With the appearance of the rash the chest cleared and remained clear throughout the period of the acute illness. As the rash cleared, the chest findings and respiratory symptoms recurred. The eczema, which had cleared, recurred and was of greater intensity than at the time of the child's first observation in August, 1947. Under continued allergy management both the pulmonary symptoms and the eczema showed improvement.

Note: This case illustrates the influence of measles on the course of asthma. In this case, the measles was severe as contrasted with the illness in Case 1.

CASE 3.—C. S., a 7-year-old female child, was first seen on Dec. 12, 1946, with a complaint of asthma. The history dated back to the age of 2 years when the child suffered with frequent head "colds," with a running and blocked nose accompanied by a paroxysmal cough lasting for several weeks at a time. In 1944, the patient had a tonsillectomy and adenoidectomy following which there was an improvement in symptoms for three months, after which period the cough returned. In April, 1946, the first wheezing was noted. This was accompanied by cough, difficult and rapid breathing with an elevation in temperature. Attacks occurred about every month lasting for three days and were usually nocturnal in character. For two weeks prior to the time of her first visit the child had asthmatic attacks every night and was comparatively free from symptoms during the day. On December 10 and 11, 1946, the child suffered with asthmatic symptoms which occurred both day and night. All attacks were preceded by a blocked nose and a dry cough.

On physical examination the child was well developed and fairly well nourished. The conjunctivae were injected. The nasal mucosa presented a bluish pallor; the turbinates were very edematous producing obstruction on both sides of the nose. The tonsils were absent. There was no regrowth of the lymphoid tissue. There was no cervical adenopathy. The chest presented no deformities. Respiratory movements were normal. Resonance was not impaired and on auscultation many coarse and sibilant râles were heard both anteriorly and posteriorly. Expiration was prolonged. The heart, abdomen, and skin were negative. A nasal smear was positive for eosinophiles.

On intradermal testing the child reacted to all the important environmental factors and the common local pollens. Management consisted of environmental control and treatment with both a pollen and an epidermal antigen which were started on Jan. 21, 1947. The response was good; the child's symptoms were controlled. The child was free from asthma until March 26, 1947, when she developed an acute attack of asthma lasting for three days after playing with a dog and rabbits. Her symptoms were again under control by removing the environmental factors. The child was symptom-free until May 21, 1948, when she developed acute asthma which did not respond to the

usual medical management (saturated solution of potassium iodide, ephedrine hydrochloride, theophylline, ephedrine, phenobarbital combined, and adrenalin hydrochloride 1-1,000). On May 28, 1948, the child had a temperature of 101° F. orally. At that time Koplik spots were observed on the buccal mucosa. The child had a harassing cough and had difficulty in breathing. Examination of the chest revealed scattered rhonchi and sibilant râles distributed both anteriorly and posteriorly throughout both lung fields. Expiration was prolonged. The symptoms showed a marked response to 0.4 c.c. of adrenalin but recurred within a few hours. On May 29, 1948, the exanthem of measles appeared and with the appearance of the rash the respiratory symptoms improved and the chest showed clearing. The chest remained clear for one week after the rash faded when the asthma recurred with coughing, labored respiration, recurring rhonchi, and wheezes. Since her measles, the child suffered intermittent asthma until Oct. 8, 1948, when she again showed improvement. Her asthma was again under control.

Note: This case illustrates the influence of measles on the course of asthma. Recrudescence does not always coincide with clinical convalescence. In this case asthma recurred one week after recovery from measles.

CASE 4.—L. T., a female child 6 years of age, was first seen in the Allergy Clinic of the children's Hospital on May 21, 1948, with a complaint of asthma since the age of 2 years. There was a history of eczema in early infancy which persisted until 2 years of age. The first asthma occurred almost immediately after the eczema cleared. The attacks of asthma which were characterized by labored respiration, coughing, and wheezing were about three days in duration, and were ushered in by running nose, sneezing, and coughing. The attacks were relieved by adrenalin. During the interval between the asthmatic attacks, the child suffered with sneezing in the morning, a running nose, and a loose productive cough which was worse at night. In February, 1948, the patient was hospitalized with a diagnosis of "bronchopneumonia" and asthma which responded to hydration and penicillin. Two weeks prior to the first clinic visit, the child had chickenpox with complete disappearance of her symptoms of allergy during the period of eruption with recurrence of asthma one week after convalescence. On physical examination the child was well developed, but poorly nourished. The palpebral conjunctivae were granular and pale. The nasal mucosa was pale and boggy. There was considerable mucoid discharge. The chest was symmetrical and the movements were free. The lungs were filled with coarse rhonchi and asthmatic wheezes. No dyspnea was observed. The heart, abdomen, and skin were negative. A diagnosis of asthma and allergic rhinitis was made.

The child was submitted to routine skin testing. On June 28, 1948, during the period of testing, the child developed a temperature of 100.4° F. rectally and showed a macular eruption of the pharynx with Koplik spots on the buccal mucosa with scattered rhonchi and squeaks throughout the chest. On July 1, the child developed an exanthem of measles simultaneously with which the respiratory symptoms improved, the lungs became clear and remained clear for two weeks after convalescence when the asthma recurred with attacks occurring practically every night. The lungs were constantly filled with rhonchi and asthmatic squeaks.

On July 22, 1948, skin tests were resumed. The child reacted strongly to intradermal tests with the environmental factors. Accordingly, environmental control was outlined and an epidermal antigen was started on Aug. 19, 1948. The child reacted with asthma to even doses of .05 c.c. of a 1:500,000 dilution. Intradermal therapy was started. Treatment was commenced with

.025 c.c. of 1:500,000 dilution intradermally increasing gradually by weekly intervals to 0.1 c.c. of 1:500,000 dilution. When the child reached a level of 0.1 c.c. of 1:500,000 dilution intradermally the child showed control of her asthma.

Note: This case illustrates the influence of both chickenpox and measles on the course of asthma. The child was symptom-free for two weeks after recovery from measles; when asthma recurred it was more severe and more constant than prior to the measles.

CASE 5.—R. B., a 10-year-old male child, first attended the Allergy Clinic on April 12, 1948. The patient was a very mild spastic, mentally-retarded child with congenital heart disease. During the first year of life he suffered a mild eczema following which he developed a severe allergic rhinitis which was perennial in character. In August, 1948, the patient developed measles which was preceded by an aggravation of the nasal symptoms producing almost complete nasal obstruction. During the period of the exanthem he was able to breath freely through his nose which he had been unable to do for several years. One week following the measles the nose again became blocked with a severe allergic rhinitis. Skin testing revealed significant reactions to environmental factors.

Note: This case demonstrates the influence of measles upon the course of allergic rhinitis.

CASE 6.—J. C., a male child 6½ years of age, was first seen on July 9, 1946, with a complaint of asthma since 2 years of age. Following the onset of the asthma, the child had attacks about every two or three months of two to three days' duration. The attacks were characterized by sneezing, running nose, coughing, wheezing, and labored respiration. The symptoms were perennial with no seasonal changes.

He suffered itching of the eyes and injection of the conjunctiva. The nose was stopped perennially and was accompanied by itching, sneezing, and a clear mucoid discharge. He was subject to occasional upper respiratory infections with swelling of the cervical glands.

On physical examination the child was well developed and fairly well nourished. There was scaling of the palpebral margins and granulation of the palpebral conjunctiva. The nasal mucosa was pale and boggy with considerable mucoid discharge. The tonsils were small. The postpharyngeal wall showed a moderate degree of lymphoid studding. There were enlarged cervical nodes bilaterally. Examination of the lungs revealed normal breath sounds with a few coarse rhonchi scattered over both sides. Otherwise the physical examination was negative.

On intradermal testing, the patient reacted strongly to pollens and environmental factors and a few foods—cow's milk Casein, string beans, banana, and peanuts.

During the winter of 1947, the child was treated with a pollen antigen, strict environmental control, and elimination of the positive food factors. During this period he suffered with repeated attacks of upper respiratory infections accompanied by temperatures of 101° F. to 103° F. orally. During the infection, the cervical nodes became swollen and the child suffered with severe asthma. The asthma responded only temporarily to adrenalin (0.4 c.c. 1:1,000 adrenalin hydrochloride) but showed a good response to treatment with the antibiotics.

After Feb. 24, 1947, he had no upper respiratory infections, but the cervical nodes remained large. Attacks of asthma occurred less frequently.

Between May 26 and June 23, 1947, he was entirely free from asthma. On June 7, 1947, a tonsillectomy and adenoidectomy were performed. Following surgery the child showed a marked improvement—his appetite increased, his nutrition improved, and by Oct. 24, 1947, he showed a gain of 11 pounds in weight. He was free of asthma until October 27, when he again developed intermittent attacks of asthma which failed to respond to the usual medication. Coughing became paroxysmal, was worse at night, and was accompanied by flushing of the face and vomiting. Between November 10 and November 26, the paroxysmal nature of the cough became more evident but the chest was clear and the child suffered no asthma. On November 10 a blood count revealed 34,750 leucocytes of which 74 per cent were lymphocytes. On November 26, the count was still 17,100 leucocytes with a definite increase in lymphocytes. By December 19, the paroxysmal cough had subsided.

On Jan. 15, 1948, the child complained of paroxysms of sneezing with slight fullness of the nose. On physical examination the nasal mucosa, which during the period of the paroxysmal cough appeared normal, now presented a pale boggy appearance with considerable mucoid discharge. Examination of the lungs revealed scattered wheezes but there was no dyspnea. From that date the child suffered a recurrence of his asthma.

Note: This case illustrates the influence of pertussis upon the course of asthma. Although the child had severe paroxysms of cough, the chest remained clear during the height of the infection.

CASE 7.—R. D., a male child 4 years of age, was first seen on Jan. 9, 1946, with a history of eczema since 3½ months of age. The eruption was erythematous, scaly, and exudative with intense itching involving the face and entire body but most intense on the arms and legs especially the flexural folds of the arms and legs. The rash was perennial with no periods of remission. There was no history of wheezing but there was some sneezing and itching of the nose.

On intradermal testing the child reacted chiefly to the environmental factors. Under environmental control and treatment with an epidermal antigen, the eczema cleared by April 26, 1946. The skin remained clear until Dec. 18, 1947, when the eczema recurred on the extremities. Ten days later, the child developed a temperature of 100.8° F. rectally. The eczema cleared and lesions of chickenpox appeared. On Jan. 8, 1948, the chickenpox started clearing and five days later, eczema recurred involving the extremities accompanied by intense itching.

Note: This case illustrates the influence of chickenpox on the course of eczema. The illness with chickenpox was mild. Temperature was never over 100.8° F. rectally, and the eruption was of moderate degree.

CASE 8.—W. D., a male child aged 14 months, was first seen on Nov. 17, 1947, with eczema involving the legs and arms, flexural folds of all extremities, and the face. Eruption was dry, scaly, nonexudative, and very itchy. Except for nasal itching there were no respiratory complaints. During the winter of 1947 he had some mild wheezing and cough and also six upper respiratory episodes without fever which were diagnosed as allergic rhinitis.

The child was tested and reacted chiefly to the environmental factors. He was placed on strict environmental control and treatment with an epidermal antigen with a good response of his skin condition. On Dec. 17, 1947, the eczema became aggravated presenting for the first time considerable exudate, crusting, pustules, and edema. He failed to respond to routine management. On December 28, the child developed a temperature of 103° F.

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rectally. The eczema was practically entirely clear and lesions of chickenpox appeared. Then there was intense itching of the lesions of chickenpox. On Jan. 5, 1948, the chickenpox cleared immediately following which the eczema recurred and presented a degree of severity equaling that just prior to the establishment of the chickenpox.

Note: This case illustrates the influence of chickenpox on the course of eczema. In contrast with Case 7, this child suffered a severe chickenpox with temperature elevated to 103° F. rectally and a very diffuse eruption of chickenpox. Cases 7 and 8 demonstrate that severity of infection is not the determining factor in influencing allergy.

CASE 9.—B. B., a 4-year-old female child, was first seen on Feb. 10, 1947, with a complaint of nasal itching, sneezing, and constant mucoid discharge. For a month preceding her initial visit, the child suffered redness and itching of the eyes. The symptoms were perennial with definite seasonal exacerbations beginning in April and continuing in July and then recurring in September.

On physical examination the conjunctivae were injected. The nasal mucosa was pale with turgescence. The turbinates were edematous. The tonsils were moderately enlarged but smooth. The uvula was edematous. There was considerable postnasal drip. Heart, lungs, abdomen, and skin were negative. A nasal smear showed a moderate number of eosinophiles and pus cells. On intradermal skin testing, the child showed strong reactions to chicken and goose feathers, cattle and dog hair, and house dust, as well as the important local pollens. Environmental control was advised and treatment instituted with a pollen antigen.

The child showed excellent control of her symptoms to the above management. Beginning on Feb. 22, 1948, the child developed severe symptoms of allergic rhinitis with nasal itching, considerable stoppage, and mucoid discharge. The lesions of chickenpox appeared. During the acute stage of the infection which lasted three days with temperatures between 102° F. and 102.6° F. rectally, the child was free of nasal symptoms. During the convalescence from chickenpox the nasal symptoms recurred accompanied by a cough. At this time her chest was clear but the nose presented a typical picture of allergic rhinitis.

Note: This case illustrates the influence of chickenpox on the course of allergic rhinitis. In this case the chickenpox was mild.

CASE 10.—R. F., a male child 7 years of age, first attended the Allergy Clinic at the Los Angeles Children's Hospital on Oct. 8, 1948, with a history of measles and chickenpox at 18 months and the onset of eczema, asthma, and allergic rhinitis at 2 years of age. All the symptoms were perennial showing no seasonal variations. At the age of 6 years, the child developed mumps with severe asthma preceding and following the parotid swelling, but was symptom-free during the parotid swelling. The eczema which had cleared since 5 years of age was uninfluenced by the parotitis.

Note: This case illustrates the influence of mumps on the course of asthma producing the typical pattern indicated in Fig. 1.

CASE 11.—B. H., a female child 16 months of age, suffered with a mild allergic rhinitis since 3 months of age. She suffered frequent attacks of sneezing, itching, with clear watery discharge. The symptoms were perennial with no seasonal variations. On physical examination there were no findings except a very pale edematous nasal mucosa with edema of the turbinates

and a clear mucoid discharge. On testing the child showed positive reactions to all the important environmental factors. She was treated with an epidermal antigen plus strict environmental control to which she showed a good response.

On Feb. 23, 1948, she had a recurrence of her nasal symptoms which persisted until February 27, when the child developed a temperature of 103° F. rectally with complete disappearance of nasal complaints. The temperature fluctuated between 103° F. and 104° F. rectally for four days. During this period the physical examination was essentially negative. The nose was clear. On March 1, her temperature dropped suddenly following which she developed a generalized fine macular morbiliform rash. A diagnosis of roseola infantum was made. A blood count done during the course of the acute illness was as follows: Erythrocytes 6,960,000, hemoglobin 74 per cent or 12.7 Gm., leucocytes 3,000 with polymorphonuclear leucocytes 26 per cent, lymphocytes 78 per cent, and monocytes 4 per cent.

On March 3, 1948, the symptoms of allergic rhinitis recurred. On examination the nasal mucosa was again pale and boggy and the turbinates were edematous. There was considerable thick grayish mucoid discharge on the floor of the nose. With continued therapy, the child's symptoms were again brought under control.

Note: This case illustrates the influence of roseola infantum on the course of allergic rhinitis. The writer has observed the same influence by roseola infantum on the course of allergic dermatitis (eczema).

SUMMARY

1. An acute infection in an allergic child may produce one of two patterns for the allergy depending upon the nature of the infection.

2. The first pattern is observed in association with pertussis and the viral infections including measles, chickenpox, mumps, Kaposi's disease, and epidemic virus infections.

3. The second pattern is observed in association with upper respiratory infections accompanied by a polymorphonuclear leucocytosis.

4. The group of diseases which produce the first pattern usually confer an active immunity after a single attack and their blood picture is a leucopenia, with the exception of pertussis which evokes a lymphocytosis. The infections which produce the second pattern confer no immunity and call forth a polymorphonuclear leucocytosis.

5. The improvement in clinical allergy by the one group of infection and the aggravation of clinical allergy by the second type of infection may suggest some studies in immunology to explain the variation in the allergic response. Such observations may help clarify the interrelationship between infection and allergy and reveal data explaining the underlying mechanisms.

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HYALURONIDASE IN PEDIATRICS

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ONE of the newer products that has given promise as a therapeutic agent is hyaluronidase.* This was first described as a spreading factor[1, 2] in 1929 and later identified as a mucolytic enzyme.[3-6] It has been obtained from numerous sources including bacteria, bee, snake, and spider venoms, leech extracts, spermatozoa, and mammalian testes.

Observations regarding its role in infection and fertilization have been formulated. Now its place in increasing fluid absorption is being investigated. The latter action has been explained by the fact that hyaluronidase is a mucolytic enzyme[3] which acts on and depolymerizes the mucopolysaccharide, hyaluronic acid. This is the gel present in the ground substance of connective tissue and acts as a tissue barrier to fluid diffusion.

With the aid of this enzyme, it has been shown[7] that fluid absorption could be increased twelvefold. In our recent report,[8] it was demonstrated that absorption was facilitated by a multiple varying from five to fourteen. The solutions used varied from normal saline, glucose in saline, Hartmann's and Ringer's solutions, to penicillin, streptomycin, adrenalin, and procaine, and the results were consistent throughout. Hyaluronidase was also tested on patients with various acute infections with elevated temperatures, and on those with allergies and with rheumatic fever, but its effect remained unchanged.

To determine its range of safety, six individuals were studied from the standpoint of its effect on urine, urine excretion, blood count, sedimentation rate, cholesterol, phosphorus, phosphatase, proteins, urea N, creatinine, sugar, icteric index, van den Bergh, and cephalin flocculation. In addition, sixteen other cases were studied in their relation to urinary and cephalin flocculation changes after daily injections of the enzyme. As far as could be determined,[8] no detectable alteration in body physiology was observed.

Skin-testing for allergic manifestations was done with the first of the products obtained, and of seventy-nine children, seven were sensitive, while of twenty-nine adults, three were positive. At that point,[8] it was felt that impurities in the product might be an explanation for this.

With our second product, there were only eight positives out of 475 cases, and when 122 (including seven of the previous allergies) were retested one month later, only two remained sensitive. The following month, only one positive was noted, and three months later out of forty that were rechecked (including the previous positive) not one allergic reaction was obtained.

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Presented at the 21st Graduate Fortnight of the New York Academy of Medicine.

*Hyaluronidase was supplied through the courtesy of Dr. Irwin G. Winter, Director of Clinical Research of G. D. Searle Co., Chicago, Ill.

Recently a more highly purified product was received and to date 105 adults and 158 children have been skin-tested with only one child revealing an allergic response. This child was negative one month before and now is sensitive to both an intradermal and subcutaneous test.

Conjunctival tests were performed on forty infants under 1 year of age, on eleven children from 4 to 12 years (including the previous positive reactor), and on fourteen adults. Not one sensitivity was observed with readings at fifteen and thirty minutes and also at one and twenty-four hours. This interesting result, although not conclusive since it was only noted in one case, indicated that the skin test appeared to be more sensitive than the eye test.

In summarizing these results (Tables I and II), there have been 1,048 skin tests with twenty-two positives for a 2.1 per cent with the probabilities that the figure will be reduced as more tests are done with the latest purification of the product.

TABLE I. HYALURONIDASE SKIN TESTS

	FIRST GROUP	SECOND GROUP	THIRD GROUP	TOTALS
Adults				
Number	29		105	134
Number positive	3		0	3
Per cent positive	10		0	2.2
Children				
Number	79	475	112	666
Number positive	7	8	0	15
Per cent positive	8.9	1.7	0	2.3
Tests Repeated				
1 Month				
Children		122	46	168
Number		(Included 7 previous positives)		
Number positive		2	1	3
Per cent positive		1.6	2.2	1.8
2 Months				
Children		40		40
Number		(Included 2 of previous positives)		
Number positive		1		1
Per cent positive		2.5		2.5
3 Months				
Children		40		40
Number		(Included previous positive)		
Number positive		0		0
Per cent positive		0		0
Totals				
Number	108	677	263	1,048
Number positive	10	11	1	22
Per cent positive	9.3	1.6	0.4	2.1

TABLE II. HYALURONIDASE CONJUNCTIVAL TESTS

	UNDER 1 YR.	4-12 YR.	ADULTS	TOTAL
Number	40	11	14	65
Number positive	0	0	0	0
Per cent positive	0	0	0	0

Once the harmlessness of hyaluronidase was verified, clyses utilizing it were started and to date we have used it in fifty cases. Each one received from 40 to 320 μg depending directly on the duration and severity of the case. When hyaluronidase was given, the same area could be used with good absorption even up to five days. It worked best during the first clysis with gradually diminishing effect as others followed. When given over the medial aspect of the thighs, some patients developed edema of the scrotum which quickly subsided with the absorption of the fluid.

In the average case, 250 to 300 c.c. of electrolytic solution could be rapidly given within eighty minutes when utilizing hyaluronidase and other clyses could be given in fairly rapid succession. Previous to its use, a similar clysis took 150 to 180 minutes and the area could not be used again for about eight hours. Thus its use should result in quicker fluid correction and greater amount of fluid absorption per unit of body area.

In estimating the probable capacity of hyaluronidase, it was found that each microgram could take care of from 10 to 50 c.c. of electrolyte solution. The same area was used for as long as eight days in one case, but rarely was it necessary to continue for that length of time. The needles were kept in one position for five days in two cases, four days in six cases, and three days in four cases, with the remainder being in place for 1 or 2 days. Since the tissue became inflamed around the point of insertion of the needle, after the second day in most cases, it was deemed advisable to change its site every third day, but the same area could still be used if necessary.

Increasing the dose of hyaluronidase did not increase its effect in proportion to its increment. This was demonstrated in five patients, who were each given 150 c.c. of 5 per cent glucose in saline in each thigh. The comparison was made between a 20 μg dose on one side and a 40, 80, 100, 200, and 300 μg dose, respectively, given on the opposite side. In each one, the fluid was run in within one hour and while absorption was complete in sixty minutes on the 20 μg side, it took only forty-five minutes on the 40 μg side and twenty-five to thirty-minutes on the 80, 100, 200, and 300 μg sides, indicating that it would be wasteful and nonbeneficial to increase the dose above 80 μg per area per dose.

In addition, plasma was given subcutaneously in seven cases with gratifying results. First a volunteer was given 50 c.c. of plasma in one thigh and another 50 c.c. with 20 μg of hyaluronidase in the other. In the latter, induration was gone in five minutes, while the former lasted one hour. Following that, it was used in six other cases with the observation that it facilitated absorption and was even more effective when the plasma was diluted with saline in a 1:1 ratio. In one infant with severe diarrhea, a local pocket of boggy edematous tissue formed and absorption was delayed. Examination revealed a total serum protein of 4.7 per cent. As soon as plasma was given intravenously, the fluid absorbed and further clyses were also absorbed with-

out any trouble. This case suggested that marked alterations in intracellular structure, plus intercellular changes could hinder the absorption despite the hyaluronidase.

Its effect on the administration of subcutaneous or intramuscular blood was also studied in three cases. In a 1-year-old female infant with malnutrition and anemia, 100 c.c. were given with 20 μg of hyaluronidase in each thigh. At a rate of 12 to 16 drops per minute, it was completed in three hours, with only slight evidence of swelling and erythema which was gone in two hours. In another case, on the first day blood was given diluted one and one-half times with saline, on the second day with equal parts of saline, and on the third day undiluted. The hemoglobin rose from 6.6 Gm. to 7.5 Gm. with the most noticeable improvement after the whole blood. In the third case, blood was diluted with equal parts of saline and the hemoglobin increased from 10.5 Gm. to 12 Gm. It appeared during the administration that when the blood was diluted, the hemoglobin did not rise much because the blood volume was probably increased and diluted by the saline; but with undiluted blood, the effect was more marked.

Its effect was also studied in two cases of hydrocephalus with the hope that intraventricular instillations would prevent progressive increase in the size of the skull. While the circumference did not increase during its administration, there was only a slight but not a very material decrease. One of the patients received 145 μg in ten days and the other 900 μg in sixty days. No ill effects were noted and this would tend to reaffirm the apparent wide range of safety of this drug.

SUMMARY AND CONCLUSION

1. Hyaluronidase was used subcutaneously in sixty cases, of which fifty were with electrolytes, seven with plasma, and three with blood.

2. It definitely facilitated absorption in all cases.

3. Its effect on intraventricular fluid in hydrocephalus was indefinite and requires further investigation, but the dosages used proved the drug's relative lack of toxicity.

4. Skin-testing only revealed a 2.1 per cent of sensitivity, with the percentage decreasing as more purified products were used. Furthermore, only one child had apparently acquired sensitivity to the product when rechecked, while seven allergies became nonsensitive after three months.

5. Conjunctival testing has failed to reveal any reaction to date but appears to be inferior to skin-testing for this product.

6. In view of its demonstrated harmlessness, and because of its apparent effectiveness, hyaluronidase should be a useful aid in the administration of fluids by elysis.

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ASSOCIATED FACIAL AND INTRACRANIAL HEMANGIOMAS

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HORROCKS,[1] in 1883, reported the case of a 9-year-old mentally deficient boy who had a vascular nevus of the right side of the face, a network of vessels over the sclera, and tortuous retinal veins. Since birth the child had suffered seizures involving the left side of the body and had developed left-sided hemiplegia with contractures of the left arm. Horrocks postulated the presence of an angiomatous malformation of the pia mater on the right side as the cause of the convulsions. In 1897 Kalischer[2] described a patient with a similar history and comparable physical findings. At autopsy an extensive venous angioma of the pia was found and the left hemisphere proved to be smaller than the right. Volland[3] later reported a patient exhibiting the same clinical picture in whom, in addition to a pial angioma, there was found calcification in the cerebral cortex. In 1921 Wissing[4] called attention to a singular shadow demonstrable by x-ray in the occipital region of an epileptic who had a vascular nevus of the face. The first published account of a similar finding was by Weber[5] in 1922. The x-ray shadow was believed to be due to calcification in the pial vessels until Krabbe,[6] in 1932, showed that the deposits in such cases were in the cortex, not in the pial angioma. His microscopic findings resembled those of Volland. Cushing[7] was the first to describe cases of this disorder in the American literature.

This association of facial and cerebral angiomas, with or without epilepsy, cortical calcification demonstrable by x-ray, and eye symptoms, has been given a variety of names: the Sturge-Weber or Sturge-Weber-Dimitri syndrome, Sturge's disease, Krabbe's disease, Kalischer's disease, the Brushfield-Wyatt syndrome, neurocutaneous syndrome, encephalotrigeminal angiomatosis, nevoid amentia, and the cerebrocutaneous syndrome. In the literature available to us we have found 192 cases. This number does not include those reported as abortive type, in which either the facial angioma was not present or evidence of meningeal involvement was not shown.

CASE REPORT

F. C., a 2-year-old white female child of Italian-American parentage, was referred to the Boston Floating Hospital because of convulsions. The family history is of interest in that two paternal cousins have "birthmarks," one on the forehead, the other on the posterior neck. Two siblings are normal.

The child was born in a local hospital after a full-term pregnancy which was uneventful except for a great deal of vaginal bleeding. Delivery was aided by forceps after two to three hours of labor. At birth the infant appeared to be normal in all respects save that a port-wine nevus was present over the right

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side of the forehead. The neonatal period was uneventful. The child sat up at 6 months of age, stood and walked at 13 months, talked at 14 months. About one and one-half months before admission a moderate amount of bright red blood had appeared in her stools on a few occasions. She was said to be always very irritable and to cry a great deal without apparent cause.

At the age of 13 months there occurred a convulsion which lasted about one-half hour and was confined to the left side. At 19 months a second seizure occurred, similar to the first in character and duration. Before each episode, according to the family physician, there was evidence of an upper respiratory infection and a rise in temperature. Five days before admission she became more irritable than usual and developed a fever. While in the office of her pediatrician she vomited and had a left-sided convulsion which lasted nearly an hour. During the next few days she was very listless. On the day preceding admission her mother noted many episodes of "staring into space," during which the child's attention could not be gained. On the morning of admission there were several similar attacks. Between them she was apparently in possession of her faculties but showed little animation. Late in the morning she vomited, became stiff, and turned blue. One hour later, while in another hospital, a left-sided convulsion started and she was then brought to this hospital. Her father stated that each convulsion had begun with twitching on the left eye and the left corner of the mouth. The seizure then spread to the left hand and arm and then to the left leg. The head and eyes had always been turned to the left.

On admission her temperature was 100.4° F., pulse 92, respirations 30. She was in a continuous seizure which involved only the left side. There were twitching of the left lids and cheek and clonic movements of the left extremities. Three hours after its onset the convulsion was controlled with ether after all other methods had failed. Examination some time later revealed an attractive, well-developed child. The head was normal in size, symmetrical, and well shaped. There were no pulsations or bruits over the skull. A dusky rose, smooth, flat nevus extended from the margin of the upper lid on the right to the vertex and laterally to the extent of the eyebrow. It did not cross the midline and involved only a small portion of the nose. Its distribution was thus confined within the limit of the ophthalmic branch of the trigeminal nerve. The eyes were normal in size and did not protrude. The pupils were round, regular, and equal and reacted normally to stimuli. The sclera and conjunctiva were normal, as were extraocular movements. Fundoscopic examination showed the discs to be sharply outlined and there was no overgrowth, tortuosity, or dilatation of the retinal vessels. Vision apparently was normal. There was no angiomatous involvement of the nasal or buccal mucosa. The teeth were in good condition except for an enamel defect of an upper incisor. The lungs were clear. The heart was unremarkable except for a soft systolic murmur in the fourth left interspace near the sternum. Abdomen and external genitalia were normal. A rectal examination demonstrated no pathology. The extremities were of equal length and circumference. Muscle tone was normal. Tendon reflexes were three plus and equal. Plantars were flexor. Gait, station, and sensation were normal. The skin of the trunk and extremities was without blemish except for a small *café au lait* spot on the right lower abdomen.

Laboratory Data.—The urine was negative. The cellular constituents of the blood were within normal limits, as were the calcium, phosphorus, phosphatase, nonprotein nitrogen, and cholesterol. The cerebrospinal fluid four hours after cessation of the seizure was under normal pressure and was clear. Protein, sugar, and chlorides were normal in amount. A tuberculin test was negative. X-ray examination of the chest showed no abnormalities. X-ray examination

of the skull showed no abnormalities of the bony structure or signs of increased intracranial pressure. In the left side of the cerebellum was seen a 4 mm. rounded and sharply delineated area of calcification, the central portion of which was more radiolucent than the more peripheral portion. A pneumoencephalo-

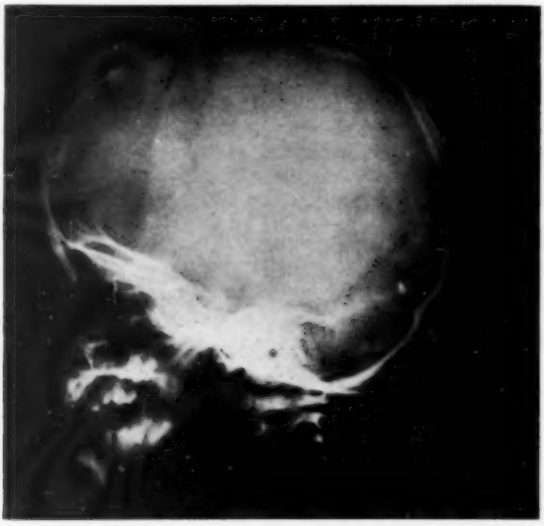

Fig. 1.—Lateral view of skull showing calcification in left cerebellum.

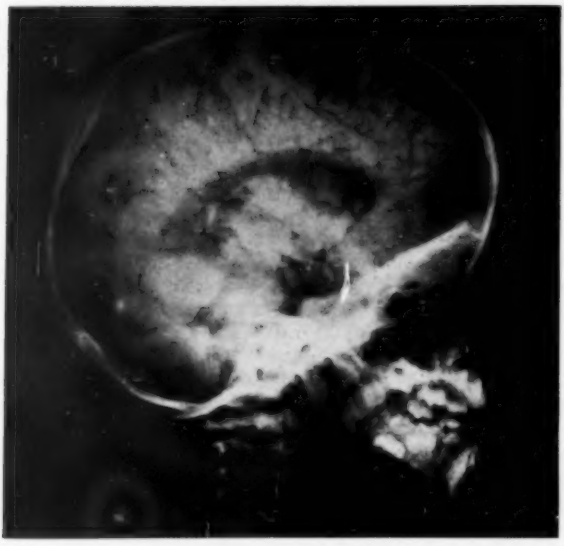

Fig. 2.—Lateral view of pneumoencephalogram showing calcification in the left cerebellum and slight dilatation of the ventricles.

gram was done following the introduction of 80 c.c. of air. The ventricular system and brain surface were well visualized. There was slight but definite dilatation of the entire ventricular system, including the fourth ventricle and the cisterna magna. There was no evidence of a filling defect or shift of the intracranial contents. From this study it was concluded that there was mild but definite deficiency of cerebral and cerebellar tissue probably associated with a small mass in the left cerebellum, possibly an hemangioma. An electroencephalogram showed definite focal slow wave activity occurring in the right hemisphere, most marked in the motor and occipital regions and suggesting localized pathology. Because of the earlier episode of melena, a barium enema and upper gastrointestinal series were done to demonstrate a possible angioma. These were negative. The child's I.Q. on the Revised Stanford-Binet test was 100.

The patient's hospital course was uneventful. She exhibited post-ictal somnolence for several hours and then was very irritable for a few days. Her disposition gradually improved, although she was prone to short temper tantrums on slight provocation. There were no further seizures.

For the following six months the child was followed by her pediatrician. Her health was excellent during the period and she received no medication. To her parents she appeared to be normal. She was returned to this hospital at the expiration of the term. At that time there was no change in the physical findings. X-ray examination of the skull showed the cerebellar calcification to be unchanged. An electroencephalogram was interpreted as showing a basically slow pattern, normal for age. Because of movements the record was unsatisfactory. A right carotid cerebral angiogram was done at the Children's Hospital. The films showed the internal carotid artery to be well filled and normally placed. The middle cerebral artery was well visualized and rose in normal fashion. The anterior cerebral artery was not satisfactorily visualized, apparently due to nonfilling, the cause of which was not clear. To the viewer it did not seem likely to presuppose an anterior cerebral thrombosis on this basis alone.

COMMENT

This case illustrates four of the five cardinal features of the condition: nevus over the trigeminal area, seizures of the Jacksonian type, intracerebral calcification, and psychic disturbance. Ocular abnormalities did not appear. The area of calcification was unusual in that it appeared in the cerebellum. Whether or not there are deposits in the cerebral cortex which are not dense enough to be demonstrable by x-ray examination, it is naturally impossible to say. It was expected that the cerebral angiogram would show evidence of an angioma over the right hemisphere but, except for the nonfilling of the anterior cerebral artery, the cause of which is speculative, the findings were normal. This does not indicate, however, that an angioma over the hemisphere is not present. It is believed that we are dealing here with one of a diffuse capillary type not shown by this technique.

CLINICAL AND LABORATORY FINDINGS

The condition has been discovered in all age groups, the first signs appearing in most cases, however, in early childhood. Boys are somewhat more frequently affected than girls. Heredity appears to play a part in some instances, although the evidence for this is slight. The nevus is usually of the flat, port-wine variety,

and is smooth, although it may be cavernous, rough, warty, or thickened and cause marked asymmetry of the facial structures. It is practically always within the distribution of one or more branches of the trigeminal nerve and in the great majority of cases is unilateral. The size varies. The whole trigeminal area may be involved or only a small portion of one or all divisions. Instead of a typical nevus there may be merely dilated or pulsating vessels. Except in rare cases the facial and cerebral angiomas are on the same side. In one of Oppenheim's[8] patients the nevus was on the left side of the face and the seizures involved the same side of the body, indicating that the cerebral pathology was probably on the opposite side. He offered three possible explanations for this: (1) reflex epilepsy, (2) spread of the angioma to the opposite side, and (3) failure of pyramidal crossing. In the case of Vincent cited by Weber[5b] contralateral angiomas were demonstrated at autopsy. In some cases other elements enter the make-up of the facial lesion. In the case reported by Greig,[9] for example, the type of telangiectasis seen in tuberose sclerosis was found. In two of the cases reported by Yakovlev and Guthrie,[10] polypi resembling those found in neurofibromatosis were associated with the nevus. The buccal and nasal mucosa may be involved, with epistaxis a prominent symptom. Other portions of the body surface are commonly affected, the side bearing the facial lesion as a rule most extensively. The lungs, liver, kidney, and intestines have shown associated hemangiomata. In our patient melena indicated the possibility of an intestinal lesion but this could not be demonstrated by barium study.

Convulsions occur in slightly more than 75 per cent of cases. They are usually Jacksonian but may be generalized, or they may be Jacksonian early, later becoming generalized. Petit mal-like episodes are not uncommon. The first seizure occurs in infancy in most cases. Subsequent convulsions may be suffered infrequently with long free periods or regularly at short intervals. There is nothing characteristic in the seizure picture. Status epilepticus may occur terminally. In many patients, as in ours, a rise in temperature accompanies or precedes the seizure. Hemiplegia or monoplegia with resulting atrophy and contractures is often seen, or there may be transient weakness of one or more of the extremities following a convulsive episode. Hemiplegia may occur without convulsions, becoming apparent shortly after birth or when ambulation is first attempted. Thrombosis or rupture of a vessel in the cortex is the usual explanation. The electroencephalograph has been employed in relatively few cases, the most common finding being a slow wave focus on the side affected by the nevus.

The intracranial calcification is demonstrable roentgenographically in about 50 per cent of cases of this disorder. It may be present without being visible, however, for in some instances autopsy or operation has demonstrated concretions after negative x-ray reports.[11] Usually it presents the aspect of sinuous, double contoured lines which seem to follow the outline of the cerebral convolutions. It may appear in the form of a single, sharply delineated shadow or as few or multiple flecks or granules. The occipital lobe is the most frequent area of election, but the frontal, temporal, and parietal lobes may be involved singly or in combination. Cerebellar localization is extremely rare and indicates an

associated angiomatous process in that area. The concretions appear on the same side as the facial nevus, although this did not hold true in our patient or in that of Wissing.[12] In only very few cases have serial x-rays been taken, so that it is impossible to state the speed of progression of the calcifying process. In one case reported by Anderson[13] there was a considerable increase in a period of three years. The x-ray often reveals the bony structure overlying the angioma to be thickened. The diploi may be widened. In some cases the frontal sinus on the affected side is larger than its opposite. Pneumoencephalograms have been performed in a number of cases, usually with results indicating cortical atrophy on the side involved in the angiomatous process.

Lumbar puncture, as would be expected, is productive of normal findings except for rare instances of elevated pressure.

Ocular abnormalities are found in some 70 per cent of these patients. As a rule the affection is unilateral, occurring on the same side as the nevus. There may be angiomatous changes in the sclera, conjunctiva, or retina. Buphthalmos or glaucoma is common, with varying degrees of impairment of vision. Homonymous hemianopsia, retinal pigmentation, iris atrophy, heterochromia, optic atrophy, pupillary abnormalities, coloboma, strabismus, disturbances of the reflex mechanisms, and nystagmus may be found singly or in various combinations.

Psychic disturbances are reported in approximately 50 per cent of cases, ranging in severity from poor memory, inability to concentrate, or behavior disorders, to idiocy and dementia. In many cases the mental defect seems to depend upon the frequency of the convulsions, deterioration resulting from repeated severe seizures. In others the defect is possibly primary.

Endocrine disturbances have been mentioned in connection with the syndrome. Safar's[14] patient was a 28-year-old man with female distribution of hair, sparse beard, and hypoplasia of one testicle; that of Fedoroff and Bogorad,[15] a 23-year-old woman with no menses after the age of sixteen, little hair on mons or in axilla, and undeveloped breasts. The patient reported by Weber[5] was a 22-year-old woman who was obese, had infantile sex characteristics, had no pubic or axillary hair, and had not menstruated. In a number of cases in young boys adiposogenital dystrophy is described, but in no case is evidence offered that the patient's appearance was not due merely to juvenile obesity.

PATHOLOGY

Pathologic findings at operation or autopsy have been fairly uniform. When the skull is opened the dura is usually found to be thickened and unusually vascular on the affected side. The pia is the site of an angioma of varying size and character or the vessels are merely increased somewhat in number or widened. The occipital area is most markedly affected, although the temporal, parietal, and frontal areas may be involved. The cerebellum is rarely affected. Beneath the vascular defect the cortex is shrunken. The gyri are flattened, small, and feel hard to the touch. On section, if calcification is present, it appears as a ribbon running through the cortex or as chunks separated by gliosed tissue. If not seen macroscopically, the cut surface may yet feel gritty. Owing to

cortical atrophy the ventricle on the affected side is dilated. There may be angiomata found in the brain substance. Areas of hemorrhage and thrombosis may be apparent. Microscopically the pial angioma is made up of endothelial-lined blood spaces. The connective tissue is small in amount. Calcification in the vessel walls is sometimes found but is not a prominent feature. The cortex beneath is thin, with diminished or absent nerve cells and increase in gliosis. Calcification is noted in all the layers of the cortex, being most marked in the second and third layers, where the normal tissue may be completely replaced. The white substance is rarely affected. The precipitate is seen within and surrounding the walls of the precapillaries and capillaries and also free in the tissue. It appears in the form of isolated beads on the vessel walls or as mulberry-like clusters completely encircling them. The lumens may be entirely obliterated, with diminution of the vascular bed. All stages of vessel involvement may be seen in a section. The concretions which lie free in the tissue are seen as irregular granules of varying shape. They seem to bear no relation to the blood vessels. All calcified areas are surrounded by glial tissue.

Microscopic examination of the affected eye often shows angiomatous involvement of the iris, and particularly of the choroid. Adhesions may be found in the angle of the anterior chamber.

PATHOGENESIS

There is general agreement that the angiomatosis is a defect of mesodermal origin and that the anomaly is a result of a disturbance in early fetal life. The association of the trigeminal nevus with angioma of the choroid, retina, and meninges is accounted for by the fact that in early fetal life the areas are in close proximity and their vascular systems arise from a common capillary sheet. As the meninges and skull develop this common vascular bed splits up into three layers of superficial, dural, and pial vessels, for the skin and the meninges respectively.[16] With continued growth of the fetus these vascular layers and the structures they supply become more and more widely separated until they assume their definitive positions.

In regard to the cortical changes, two schools of thought exist. The one holds that there is an ectodermal defect coordinated with the mesodermal dysplasia, the other that the atrophy, gliosis, and calcification are secondary to the pial anomaly. Yakovlev and Guthrie[10] believe that the gliosis is a primary process and takes an active part in the abnormality. They believe the vascular derangement to be only a more conspicuous part of a malformation which affects the cerebrum as a whole and that a developmental factor is more important in the causation of the convulsive phenomena than the vascular lesion. Krabbe,[6] Nussey and Miller,[17] and Scheinker,[18] among others, also believe the cortical defect to be primary and independent of the pial vessel abnormality. Numerous authors link the condition with neurofibromatosis (von Recklinghausen), hemangioblastoma of the retina and cerebellum (von Hippel-Lindau) and tuberose sclerosis, grouping the four conditions under the term phakomatosis and professing to see in them common elements of ectodermal and mesodermal dysplasia.[10, 19, 20]

Alexander and Woodhall,[21] Bergstrand,[22] Peters,[23] Lichtenstein and Rosenberg,[24] and Green[25] are among those who believe that the cortex is developmentally normal and that the pial anomaly is responsible for the calcification and other cortical changes and, thus, for the neurologic manifestations. Alexander and Woodhall, and Lichtenstein and Rosenberg postulate that the calcification arises as a result of incomplete interference with the blood supply of the affected areas. Disturbances of circulation within the abnormal vascular channels leads to a lowered metabolism of the underlying cortex, vascular damage, and necrosis, with subsequent influx of calcium into the area. The incompleteness of interference with the blood supply is important. Were it complete there would be no calcification because there would be no means for its deposition. Green,[25] in attempting to explain the reason why the second and third layers of the cortex are most affected in the calcification process, points out that this area normally contains more capillaries than the superficial and deep layers and, also, that this is the junction area of the central and peripheral blood supply of the brain. It is not inconceivable that such an area might suffer most in the presence of vascular anomalies.

Various explanations have been given for the production of buphthalmos and glaucoma: stasis in angiomatous vessels with consequent increase in intraocular pressure;[26] vascular changes in the ciliary body and choroid, either preventing development of the canal of Schlemm or causing blockage of the filtration angle[27]; impairment of sympathetic innervation[28-30]; increased transudation from the increased vascular tissue and diminished outflow of intraocular fluid.[31] Ballantyne[32] suggests that in some cases the angioma may be sufficiently developed in antenatal life to establish buphthalmos, while in others the growth is delayed to adult life with the production of secondary or simple glaucoma.

DISCUSSION

The clinical and pathologic findings seem to indicate that we are dealing with a purely mesodermal primary defect, an angiomatous malformation, at least in the majority of cases, in this syndrome. Were a primary ectodermal dysplasia the rule, one would expect symptoms of disturbed mentation to be more constant in incidence and severity. Instead, we find roughly 50 per cent of patients with no psychic difficulties and in many of the remainder a progression of the mental defect only as severe seizures are often repeated. There seems to be no necessity for postulating an accompanying ectodermal maldevelopment to account for the cortical changes and the neurologic manifestations. A pial angioma, like a subdural hematoma, occupies space normally provided for other structures in the intracranial economy. If large enough, there is pressure on the cortex. Added to this is the factor of circulatory derangement. Circulation within intracranial angiomas is slowed.[25, 33] As a result of this relative stasis the process of calcification, gliosis, and further atrophy as outlined by Woodhall and Alexander, and Lichtenstein and Rosenberg take place.

DIAGNOSIS

A strong presumptive diagnosis of an intracranial angioma can be made in a patient with a facial nevus who has convulsive seizures or exhibits signs of a

cerebral vascular accident. It is confirmed by the presence of intracerebral calcification demonstrated by x-ray, by angiography, or by surgical exploration.

Inasmuch as treatment, whether radiation or surgery, depends for its greatest efficacy on institution before irreversible cortical changes have taken place, an early diagnosis is important. Any child with a trigeminal nevus should be studied to rule out, so far as possible, an accompanying meningeal or cortical lesion. If the diagnosis is not made before the appearance of seizures or hemiplegia or before calcification can be seen by x-ray, extremely valuable time may have been lost. In the presence of such a condition, it is important at least to secure x-ray examination of the skull, an electroencephalographic study, and, perhaps, a pneumonencephalogram. Angiography might be advisable if facilities are available. That this latter step, in the absence of signs and symptoms, is in some cases justified, is attested to by the case of a child who was apparently normal in all respects except for a trigeminal nevus but who was proved to have an intracranial angioma by carotid angiography.[34]

SUMMARY AND CONCLUSIONS

A case of associated facial and intracranial angioma is presented, together with a brief review of the clinical and laboratory findings.

The pathology is described and an exposition given of the theories advanced as to the pathogenesis of the condition.

The defect is probably primarily mesodermal in origin, with cortical changes secondary to pressure and interference with circulation in the area lying beneath the angioma. Ocular and cerebral involvement in cases of facial nevus may depend upon the time of initiation of the mesodermal defect. Before cleavage of the primitive vascular sheet, all three structures may show vessel abnormalities; afterward, one or a combination of two.

It is important that the diagnosis be made before signs of intracranial pathology appear. To this end, electroencephalography and contrast and air studies should be considered in cases of children who have trigeminal nevi.

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CYANOSIS IN PREMATURE INFANTS DUE TO ANILINE DYE INTOXICATION

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THE majority of cases of aniline dye poisoning among infants in the past have been due to cutaneous absorption from the buttock area. Rayner[1] first reported seventeen such cases from London in 1886. It was not until thirty-four years later that a second report appeared.[2] A review of all available literature at this time reveals a total of sixty-three such cases recorded in seven reports.[1-7] In an unpublished study, Altman[8] observed ten cases in newborn infants in 1932. In addition, Stevens[9] reported two cases which were due to inhalation of a disinfectant containing nitrobenzene; Zeligs' series[4] contained one with a similar etiology.

Most of these cases have been among full-term newborn infants. There was a total of five deaths among the sixty-three cases.[6, 7] Four fatalities occurred in one outbreak,[6] and the patients all expired with bronchopneumonia (one associated with intracranial hemorrhage) about three weeks after the poisoning. Of the five fatalities, four were in premature infants.

This report is based upon a study of nine premature infants who developed aniline intoxication traced to the dye used in stamping diapers. The purposes of the report are to call attention to this important cause of cyanosis, to stress the fact that it can be prevented by simple measures, and to show that it can be treated satisfactorily even in premature infants if recognized early. It is important that knowledge of the means of preventing its occurrence be spread as widely as possible.

Aniline, $C_6H_5NH_2$, is a colorless, oily, highly refracting liquid having a characteristic aromatic odor and a burning taste. It is derived from the reduction of nitrobenzene. It turns yellow to brown when exposed to air. Although only slightly soluble in water (1:31), aniline mixes readily with alcohol, ether, benzene, or chloroform. It is used mainly to synthesize aniline dyes and in the manufacture of rubber.[10] Hospitals and day nurseries often use aniline dyes to stamp the name of the institution on diapers and other linen. Intoxication may occur from the inhalation of aniline or nitrobenzene vapors, by cutaneous absorption, or by ingestion. The most evident sign of the intoxication is a peculiar grayish cyanosis. Dulstin and associates[11] attributed this to a pigment formed in the subcutaneous tissue by aniline. The blood itself becomes dark and on exposure to air does not change to its usually bright red color. Spectroscopic examination of the blood reveals the presence of methemoglobin.

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The actual mechanism of formation of methemoglobinemia by aniline is a matter of dispute. When aniline is mixed directly with blood, methemoglobin formation is very slow, and in sixteen hours only one-half molecule of methemoglobin is formed per molecule of aniline. This has been taken to suggest that aniline can change hemoglobin to methemoglobin only after the aniline has been changed to a more active oxidizing agent. It has been postulated that paraminophenol or some oxidation product such as hydroxyphenylhydroxylamine is the substance responsible for the alteration in hemoglobin. There is also a possibility that some highly pigmented oxidation product of paraminophenol may be present in the blood and tissues and in itself may enhance the bluish color of the skin. Methemoglobin is formed from hemoglobin by the action of an oxidizing agent, and it is readily turned back to hemoglobin by an equivalent amount of reducing agent. Presumably the ferrous ion of hemoglobin is changed to the ferric ion in methemoglobin. Since less hemoglobin is then available for oxygen transport, a "functional anemia" develops.[12] Darling and Roughton[13] point out that the tissues of the body are liable to anoxemia in methemoglobinemia, not only from the loss of oxygen-carrying capacity of the blood but also because, as the amount of methemoglobin in the blood increases, the blood has increasing difficulty in releasing to the tissues whatever oxygen it contains.

In the treatment of methemoglobinemia of various etiology in adults and children, oxygen inhalation, blood transfusions, methylene blue, and ascorbic acid have been the principle measures tried. In the treatment of aniline dye poisoning in infancy all these measures except ascorbic acid have been used in the past. There has been considerable disagreement as to the value of methylene blue in combating this disorder. In high concentrations it converts the ferrous ion of reduced hemoglobin to the ferric form and methemoglobin, whereas in low concentrations it apparently reverses this process.[14] Wendel[14] found that "following intravenous injection of small amounts of methylene blue, methemoglobin rapidly disappears from the blood and is replaced by an equivalent amount of hemoglobin." Although oxygen and blood transfusions have been used empirically as supportive therapy, oxygen is of doubtful value; and Wallace[15] reported one case of methemoglobinemia due to bismuth subnitrate in which transfusion of washed red blood cells resulted in an increase of the cyanosis. Lian and associates,[16] in France in 1939, were probably first to use ascorbic acid in the treatment of familial methemoglobinemia. Ascorbic acid was subsequently used successfully by Deeny and associates[17] in England in 1943, Graybiel and co-workers[18] in the United States in 1945, and Carnrick and associates[19] in 1946. Because of the marked reducing properties of ascorbic acid, the absence of untoward reactions, and the experience of these investigators with it in idiopathic congenital methemoglobinemia, we considered it advisable to try it in our cases of aniline dye poisoning.*

REVIEW OF CASES

There were thirty premature infants in the premature station on November 10, 1946. That morning it was noted that six of these infants suddenly became

*Since this study was made, a case report has appeared in which ascorbic acid was used successfully in the treatment of methemoglobinemia due to nitrates in drinking water.[20]

ill. They had a grayish, cyanotic appearance and marked apathy. Subsequently, it was noted that three more infants in the station developed a similar but milder degree of cyanosis and apathy. The age of these nine patients ranged from 3 to 64 days (average 19 days), and the weights ranged from 1,000 to 2,015 Gm. (average 1,272 Gm.).

For a few days prior to this outbreak, a faint odor which was not impressive at the time but which on recollection seemed somewhat peculiar (resembling the odor of shoe polish) had been noted in the premature station. Subsequent investigation revealed that it had developed following an emergency requisition of a large number of diapers from the linen room. Through some delay in the routine supply, there developed a sudden urgent demand for clean diapers in the station. In an effort to comply immediately the laundry sent diapers which, through an oversight, had not been boiled after stamping. The dye used to stamp the diapers was composed of nigrosin for color and a mixture of aniline oil and oil of mirbane (nitrobenzene) as solvent. Some of the diapers were used in contact with the buttocks and others were placed around the infants' necks during their feeding periods. Furthermore, the infants were kept in the confined air space of an incubator, in which the dye may have volatilized. Therefore, both inhalation and cutaneous absorption were possible avenues for entrance of the intoxicant.

SIGNS OF INTOXICATION

All nine infants had a grayish cyanosis (six severe); four of the nine were markedly apathetic; six vomited; and five had various degrees of anorexia. All of these infants showed their first sign of intoxication within a period of forty-eight hours. (During this same period another infant became apathetic and vomited but was not cyanotic. It might be that these signs were due to aniline intoxication because of the simultaneous poisoning of the others and because the symptoms disappeared with the removal of the intoxicant at the same time as did those of the other patients. Because of the absence of cyanosis, however, the case of this infant is not included in the group of nine.) Unfortunately, it was not practical at the time to examine the blood spectroscopically for methemoglobin.

COURSE

All of the infants recovered. Five of the nine developed mild to severe bronchopneumonia between the second and fourth weeks following the poisoning. On the other hand, none of the other twenty-one infants who were in the premature station at the same time developed pneumonia.

THERAPY

Three of the premature infants who had the most marked signs and symptoms were given whole blood transfusions, oxygen inhalation, methylene blue, and ascorbic acid. Methylene blue was given intravenously once to each infant (0.1 c.c. of a one per cent solution was given in 5 c.c. of saline, a total dose of 1.0 mg). Ascorbic acid was given in doses of 100 mg. orally once to one of the three and twice to the other two. Three equally ill infants were each given

ascorbic acid, 100 mg. orally once and no transfusion, methylene blue, or oxygen. In all six cases there was rapid improvement of symptoms. The remaining three cases were relatively mild and the patients were not treated with any of these measures. Recovery in these also was prompt with removal of the dye.

The therapeutic effect of ascorbic acid is difficult to evaluate since improvement began rapidly in all cases following removal of the offending dye. There is suggestive evidence that it may have prevented the signs of intoxication in the other infants. Of the nine infants who developed intoxication, eight had received no ascorbic acid in their diet previously, and one (whose symptoms were very mild) had received 25 mg. of ascorbic acid daily for two months. On the other hand, among the twenty in the station who did not develop the intoxication (excluding one questionable case noted above), ten had received 25 mg. of ascorbic acid daily for one to eight weeks, one had received 100 mg. of ascorbic acid daily for one week, and five had received 30 to 90 c.c. of fresh orange juice daily for seven to ten days. Two of the twenty did not receive ascorbic acid, and two others were not exposed to the dye because they died from other causes on the day of admission.

DISCUSSION

Aniline dye poisoning due to cutaneous absorption or inhalation is a condition which must be considered in the differential diagnosis of cyanosis and apathy in infants. Perhaps bronchopneumonia is a delayed complication which is not clinically apparent until several weeks after the intoxication. It was present in five of the nine cases in this series. There were no deaths in this group, but of the five reported deaths, four were in prematures who expired with bronchopneumonia about three weeks after the intoxication. With early recognition, removal of the offending chemical, and prompt therapy, the prognosis of this intoxication is good even in premature infants.

In order to prevent the occurrence of aniline intoxication it is of the utmost importance that all diapers be boiled *after* they are stamped. If followed by thorough drying, this would eliminate the possibility of such intoxication. Ideally, a dye should be used which is nontoxic to the human body. Unfortunately dyes made of vegetable pigments, charcoal, or silver nitrate lack the necessary permanence and with them also washing is advisable after stamping to avoid objectionable odors. In addition, the necessity of marking each diaper individually by hand when these dyes are used adds to the expense. The use of name tapes or colored threads is also relatively expensive. Until a fool-proof method of identifying diapers is found, the best means of prevention would seem to be through a widespread educational effort warning against the danger and urging the boiling and thorough drying of the diapers *after* they have been stamped.

SUMMARY

Since 1886, there have been seven reports of aniline dye poisoning among newly born infants involving sixty-three patients. In addition, there was an unreported outbreak involving ten infants, and it is quite likely that there have

been many more either unrecognized or unreported.[21] Among these cases, there were five deaths, four of these being premature infants who died with bronchopneumonia three weeks after the poisoning.

This report is based upon a study of nine premature infants who developed aniline dye intoxication traced to freshly stamped diapers. They developed the characteristic grayish cyanosis, and five developed bronchopneumonia between the second and fourth weeks after the intoxication. There were no deaths.

The pathogenesis and treatment are discussed. Early recognition of the condition and removal of the offending chemical are essential. Ascorbic acid warrants further trial as a therapeutic measure.

The importance of and methods for prevention should be made common knowledge; laundry personnel and all other individuals concerned should be impressed with the importance of withholding stamped diapers until *after* they have been boiled.

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STUDIES ON ANTIBIOTICS IN THE CEREBROSPINAL FLUID

I. The Inhibitory Effect of Normal Cerebrospinal Fluid on the Antibacterial Action of Streptomycin

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INTRODUCTION

RECENT in vitro studies by Tucker[1] have shown that normal cerebrospinal fluid has an inhibitory effect on the antibacterial action of penicillin. It has also been demonstrated that human serum exerts a similar inhibitory action on both streptomycin[2] and penicillin.[3] A protein-binding mechanism[4] was shown to be involved in the inhibitory effect of human serum on penicillin. This is in contrast to the findings of Tucker, which suggest that penicillin is actually destroyed by cerebrospinal fluid.

In view of these facts, the question arises whether the cerebrospinal fluid exerts a similar inhibitory action on streptomycin. It is the purpose of this paper to present data designed to answer this question.*

Very little is known about the influence of cerebrospinal fluid on antibiotic agents. Some of the problems in addition to the above which deserve clarification are: (1) the effect of cerebrospinal fluid from patients with meningitis on the antibacterial action of streptomycin and penicillin; (2) the effect of cerebrospinal fluid from patients with febrile illnesses other than meningitis on streptomycin and penicillin; (3) the mechanism of the inhibitory action of normal cerebrospinal fluid on streptomycin; and (4) further observations on cerebrospinal fluid levels of streptomycin and penicillin after parenteral administration in patients with damaged and undamaged meninges. Studies on these problems are to be reported later, and will have a bearing on the controversial subject of intrathecal administration of antibiotics in the treatment of meningitis.

METHODS AND MATERIALS

Cerebrospinal fluid was obtained from seventeen patients admitted to the Children's Hospital. Most of these were brought into the hospital for elective surgery and none showed any evidence of meningeal pathology. All of the cerebrospinal fluid specimens were water-clear and none were contaminated with blood. The temperature of each patient was normal.

Bio-assay determinations for streptomycin were done by the method of Price, Nielsen, and Welch.[5] This method utilizes the inhibitory effect of streptomycin in serial dilutions on the growth of *Bacillus circulans*.† Standards were

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*Streptomycin Calcium Chloride Complex was used in this study.

†A standardized strain of *B. circulans* was obtained from the Food and Drug Administration Division of The Federal Security Agency, Washington, D. C.

prepared for each determination. Thus we were able to demonstrate the inhibitory effect of varying but known quantities of streptomycin on a constant dilution of the organism in broth. To set up these standards, ten tubes were arranged in series. One milliliter of nutrient broth was added to each of the tubes except the first. Ten micrograms of streptomycin in one milliliter of normal saline was placed in both the first and the second tubes. Beginning with the second tube, serial dilutions of streptomycin were extended through the ninth tube by transferring one milliliter of fluid to each succeeding tube. Therefore, the first tube contained 10 μg of streptomycin, the second 5 μg, and the third 2.5 μg, ending with 0.03 μg in the ninth tube. One-half milliliter of saline was placed in each of the ten tubes. This was necessary in order that comparable volumes would be present in the standard and the cerebrospinal fluid series. Lastly, one and one-half milliliters of 1:100 broth culture of *B. circulans* were added to each of the ten tubes after the dilutions were made. The tenth tube was the control tube and tested the viability of the organism, since it contained no streptomycin.

For testing the inhibitory effect of cerebrospinal fluid, three groups of ten tubes each were arranged in series. One milliliter of nutrient broth was placed in the second through the tenth tube. However, in contrast to the standard determinations, 100 μg of streptomycin were pipetted into both the first and second tubes. Then, beginning wtih the second tube, the serial dilutions were made through the tenth tube. Thus the first tube contained 100 μg of streptomycin, the second 50 μg, and the third 25 μg, ending with 0.18 μg in the tenth tube. By starting with 100 μg of streptomycin in the first tube, it was possible to test a wider range of inhibition and include the range of streptomycin concentrations in the standard series. The same quantity of the organism used in the standards was added to each tube. To one series 0.5 ml. of cerebrospinal fluid was added to each tube, to a second series 0.25 ml., and to a third series 0.1 ml. was added to each tube. Therefore, we were able to ascertain the effect of varying amounts of the same cerebrospinal fluid on the antibacterial action of streptomycin. The cerebrospinal fluid added to the tubes of the second and third series was diluted with a quantity of normal saline necessary to keep the volume and, therefore, the streptomycin concentration, constant in the corresponding tubes of each series.

The last tube in which growth of *B. circulans* was completely absent indicated the amount of streptomycin necessary to inhibit growth of the organism. These results were expressed as micrograms per milliliter, as outlined by Price, Nielsen, and Welch[5] in their original bio-assay method. It must be pointed out that the final volume in our experiments was 3 ml., whereas 2.5 ml. volumes were used by the aforementioned investigators. This variation becomes insignificant in the interpretation of our results, since, as stated prevoiusly, comparable dilutions were present in the standard and in the cerebrospinal fluid series.

RESULTS

Reference to Table I demonstrates the quantity of streptomycin necessary to inhibit the growth of *B. circulans* with and without cerebrospinal fluid.

TABLE I. THE RESULTS DEMONSTRATING THE INHIBITORY EFFECT OF VARYING QUANTITIES OF NORMAL CEREBROSPINAL FLUID ON STREPTOMYCIN USING B. CIRCULANS AS THE TEST ORGANISM*

PATIENT	AGE	STREPTOMYCIN NECESSARY TO INHIBIT GROWTH (μG/ML.)			
			MILLILITER CEREBROSPINAL FLUID ADDED		
		STANDARD	0.5	0.25	0.1
1. J. S.	8 mo.	0.6	1.5	--	--
2. A. R.	3 yr.	0.3	1.5	--	--
3. P. H.	8 yr.	0.3	0.7	--	--
4. L. S.	2 yr.	0.6	6.2	6.2	--
5. B. J. P.	7 yr.	0.6	6.2	6.2	--
6. I. M. P.	9 yr.	0.6	3.1	3.1	--
7. A. N.	8 yr.	0.3	6.2	6.2	0.3
8. M. E.	10 yr.	0.3	3.1	3.1	0.3
9. J. M.	10 yr.	0.3	3.1	1.5	0.7
10. R. R.	11 yr.	0.3	3.1	3.1	0.7
11. G. Wi.	7 yr.	0.3	3.1	3.1	0.7
12. M. A. B.	4 yr.	0.3	3.1	3.1	0.3
13. G. Wr.	6 yr.	0.3	3.1	3.1	3.1
14. M. P.	6 yr.	0.3	3.1	1.5	0.7
15. M. B.	12 yr.	0.3	1.5	1.5	0.7
16. H. S.	15 mo.	0.1	1.5	1.5	0.7
17. E. M. O.	9 yr.	0.3	3.1	3.1	1.5

*Experiments were not conducted where data are absent.

In the standards the organism was inhibited by 0.3 μg per milliliter in the majority of the instances. The range was from 0.1 μg per milliliter in Patient 3, to 0.6 μg per milliliter in Patients 1, 4, 5, and 6.

In the presence of 0.5 ml. of normal cerebrospinal fluid, the quantity of streptomycin necessary to inhibit the organism in the majority of instances was 3.1 μg per milliliter, and ranged from 1.7 μg per milliliter in Patient 3 to 6.2 μg per milliliter in Patients 4, 5, and 7. When 0.25 ml. of normal cerebrospinal fluid was added, the quantity of streptomycin necessary to inhibit the organism was 3.1 μg per milliliter in seven of fourteen patients, and ranged from 1.5 μg per milliliter in Patients 9, 14, 15, and 16 to 6.2 μg per milliliter in Patients 4, 5, and 7. The quantity of streptomycin required to inhibit growth of *B. circulans* in the presence of 0.1 ml. of normal cerebrospinal fluid was 0.7 μg per milliliter in the majority of the determinations; the range under these conditions was 0.3 μg per milliliter in Patients 7, 8, and 12, to 3.1 μg per milliliter in Patient 13.

An effect comparable to that of 0.5 ml. of normal cerebrospinal fluid was exerted by 0.25 ml. of cerebrospinal fluid on streptomycin in Patients 4 through 8, 10 through 13, and 15 through 17. However, in Patients 9 and 14 there was a decreased effect as compared with 0.5 ml. When 0.1 ml. of cerebrospinal fluid was added, a smaller but definite inhibitory effect on streptomycin was demonstrated in eight of eleven patients. This effect was not demonstrated in the remaining three patients. Such variations in any one series would be expected within the limits of accuracy of bio-assay determinations.

DISCUSSION

From the results of this study we were able to demonstrate a definite inhibitory action of normal cerebrospinal fluid on the antibacterial action of streptomycin. In the presence of 0.5 ml. of cerebrospinal fluid, it was demonstrated

that approximately ten times as much streptomycin was necessary to inhibit the growth of *B. circulans* as in the standard. The average quantity of streptomycin necessary to inhibit growth of *B. circulans* in the presence of 0.25 ml. of cerebrospinal fluid was also approximately ten times that in the standard. In the presence of 0.1 ml. of cerebrospinal fluid, approximately two and one-half times the quantity of streptomycin was necessary to inhibit the organism.

Analysis of these data suggests that there is a quantitative relationship between the amount of cerebrospinal fluid and its inhibitory action on streptomycin, since considerably greater inhibition was demonstrable in the presence of 0.5 ml. of cerebrospinal fluid than in the presence of 0.1 ml.

It is interesting that with low concentrations of cerebrospinal fluid, a definite inhibitory effect was present. These data suggest that the inhibitory mechanism, whatever its nature may be, is a relatively potent one. These facts further suggest that although some streptomycin may reach the cerebrospinal fluid after parenteral administration, it may not be detectable by present bio-assay methods. The cerebrospinal fluid may inhibit or may destroy the streptomycin in low concentration. The mechanism of this action of normal cerebrospinal fluid cannot be explained at this time.

SUMMARY AND CONCLUSIONS

1. Specimens of cerebrospinal fluid from seventeen patients with no evidence of meningeal pathology were tested for their inhibitory effect on the antibacterial action of streptomycin.

2. The antibacterial action of streptomycin is definitely inhibited in the presence of normal cerebrospinal fluid.

3. There is a suggestion of a quantitative relationship between the amount of cerebrospinal fluid and its effect on the antibacterial action of streptomycin.

4. This inhibitory action of normal cerebrospinal fluid on streptomycin may prevent the detection of antibiotics in the cerebrospinal fluid by present methods of bio-assay.

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CONGENITAL SARCOMA

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IN 1940, Wells[1] published an exhaustive review of malignant congenital tumors in which he subjected all cases reported up to that time to careful scrutiny. Because of insufficient data, 150 cases were classified by him as possible, twenty cases as probable, congenital sarcomas. There remained a group of thirty cases, including one published by Pack and Anglem,[2] which was accepted as certain. If one omits the rather frequent congenital neuroblastoma of the retina, these thirty cases represent more than one-half of all accepted congenital malignant tumors. Since 1940, no additional cases have been listed in the *Quarterly Cumulative Index Medicus*. Even assuming that a number of such tumors have been sporadically observed but remained unreported, one must consider congenital sarcoma an exceedingly rare neoplasm.

It is to be expected, therefore, that a newborn child with such a tumor presents an almost unique problem to the attending physician who most likely has never seen a similar case before. What is the degree of malignancy of such a tumor? What is the outlook for the patient? How should the condition be treated and especially can mutilating operations in an infant be avoided? Any additional experience with such lesions should be interesting so that the following case of congenital sarcoma of the foot is reported.

CASE REPORT

A white male infant (Admission No. 48,819) was born on Sept. 25, 1947, in this hospital. Delivery was at term and normal. On October 3, one week after delivery, a lump the size of a split hazelnut was noted on the back of the right foot. The family physician thought it was a ganglion and attempted to crush it, without success. Instead, the mass became rapidly larger and the baby was referred to this hospital for biopsy on November 6. An ill-defined firm mass of slightly bluish color was present on the dorsum of the right foot. It measured about 2 cm. in diameter. It was incised and diffuse pinkish-grayish glistening tissue was encountered which involved the subcutis and the dorsal tendons. Removal was impossible and a biopsy was taken. It showed a diffusely growing tumor composed of medium-sized ovoid cells with hyperchromic nuclei. Atypical nuclei and mitoses were seen. Many lymphocytes and plasma cells and a considerable amount of brownish pigment, identified as hemosiderin, were present. A diagnosis of spindle-cell sarcoma was made.

Amputation was advised, but because of the gravity of such a decision, consultation was arranged with the Memorial Hospital in New York City. The child was seen there on November 24. The diagnosis of sarcoma was confirmed and amputation of the leg recommended—exarticulation in the hip if the inguinal lymph nodes contained tumor.

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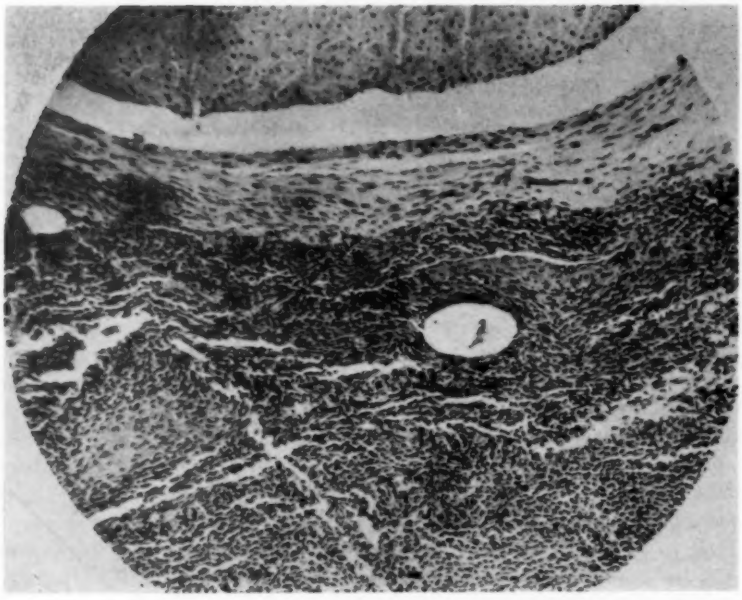

Fig. 1.—The tendon is seen on top. The tumor is in intimate relation to the tendon sheath.

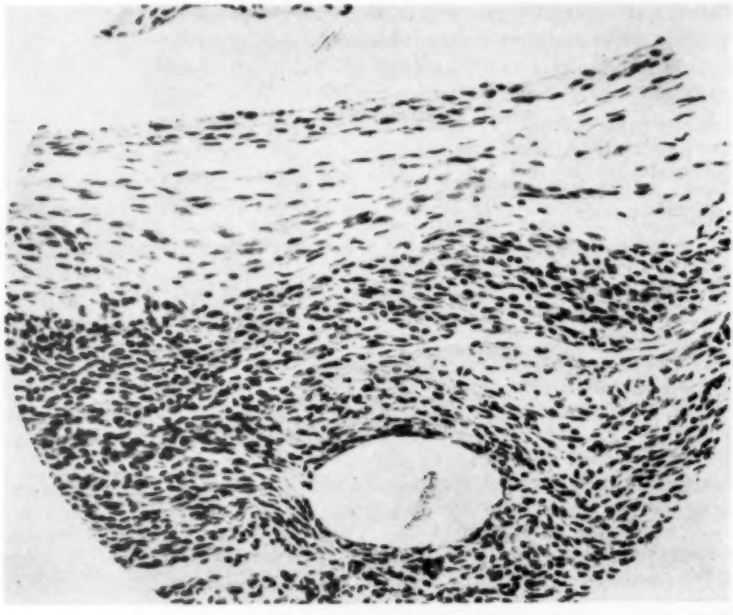

Fig. 2.—Higher magnification of the tumor. The oval space, lined with endothelium, suggests possibly an attempt to form a synovial cavity.

The right inguinal lymph nodes had become slightly enlarged following the biopsy and had been excised on November 17. They were free of tumor. Also, 900 r (3 exposures, 140,000 volt, 50 cm. distance, A. L. filter) had been given between November 15 and November 22, with the vague idea of doing something possibly useful until a final decision had been made.

Finally, amputation at mid-thigh level was performed on December 4. Operation and postoperative course were uneventful. The infant has been seen at regular intervals, the last time on Dec. 21, 1948. He has developed normally and is in good health.

The skin over the tumor area in the operative specimen was slightly pigmented and scaling. The tendons were surrounded by light brown and pinkish mottled glistening tissue. The periosteum and bone were not involved. Microscopically, the tendons were surrounded by sheathlike masses of tumor cells as described which seemed intimately connected with the tendon sheaths. Hemosiderin was present in moderate amounts. The connective tissue was somewhat edematous. No cellular changes attributable to radiation as applied were noted. The diagnosis was congenital spindle-cell sarcoma of foot, arising probably from tendon sheath.

DISCUSSION

Little need be said about the histologic aspects of this case. Slides were submitted to several prominent pathologists who all concurred on the diagnosis of sarcoma. The arrangement of the tumor cells around the tendons and their continuity with the tendon sheath suggests that the tumor developed from these structures. The hemosiderin and inflammatory reaction are attributed to the trauma produced by the attempt to crush the mass. No histologic evidence of response to roentgen rays was seen but the amount applied was too small to allow drawing any deductions regarding its effectiveness. However, all consultants agree that a tumor of this type is radioresistant.

In order to evaluate more intelligently the selection of treatment in congenital sarcoma and the prognosis attached to it, Table VII of Wells' paper was rearranged and the case reported by Pack and Anglem and the present case were added. The untreated and treated cases were separated and grouped according to the location of the tumor in the extremities or elsewhere. The treated cases were also arranged according to the type of therapy. (See Table I.)

The following conclusions can be drawn:

A. All untreated cases of congenital sarcoma die, irrespective of location and histologic type.

B. Treatment and results obtained differ sharply between congenital sarcoma located in the extremities and that located elsewhere in the body.

1. With proper treatment, the prognosis for congenital sarcoma of the extremities is excellent. Ten patients out of twelve are reported well for periods up to ten years. With the outcome unknown in one instance, there remains only one case with fatal outcome (No. 21). This patient died immediately following amputation which had been delayed until he was 16 months old. Previous prolonged roentgen therapy had proved ineffective.

TABLE I*

NO.	LOCATION	HISTOLOGIC TYPE	THERAPY	OUTCOME	REMARKS
			UNTREATED CASES		
1	Thigh	Fibrosarcoma	None	Unknown	Size of infant's head at birth
2	Thigh	Periosteal	None	Died	
3	Orbit	Round cell	None	Died	
4	Orbit	Round cell	None	Died	
5	Brain	Angiosarcoma	None	Died	
6	Neck	Angiofibrosarcoma	None	Died	
7	Skin	Round cell angiosarcoma	None	Died	
8	Pancreas	Lymphosarcoma	None	Died	
9	Small bowel	Round cell or angiosarcoma	None	Died	
10	Prostate	Rhabdomyosarcoma	None	Died	
			TREATED CASES		
			Tumor Located in Extremity		
11	Upper arm	Oat cell	Excision	Recovered	Follow-up 2 years
12	Calf	Spindle cell	Excision	Unknown	
13	Humerus	Spindle cell	Amputation	Recovered	Follow-up 10 years
14	Fibula	Spindle cell	Amputation	Recovered	Follow-up 4 years
15	Tibia	Fibrosarcoma	Amputation	Recovered	Follow-up 8 years
16	Foot	Fibrosarcoma	Amputation	Recovered	Follow-up 8 months
17	Foot	Spindle cell	Amputation	Recovered	Follow-up 1 year
18	Foot	Sarcoma	Amputation	Recovered	Not stated
19	Humerus	Periosteal	Exarticulation	Recovered	31 months
20	Femur	Spindle cell	Excision and radiation	Recovered	Not stated
21	Forearm	Spindle cell	Radiation plus amputation	Died	Died postoperative after unsuccessful radiotherapy
22	Leg	Liposarcoma	Radiation	Recovered	Follow-up 4 years
			Tumor Located in Places Other Than the Extremities		
23	Tongue	Spindle cell	Excision	Unknown	
24	Tongue	Spindle cell	Excision	Died	
25	Tongue	Round and spindle cell	Excision	Died	
26	Axilla	Fibrosarcoma	Excision	Unknown	Metastases present
27	Subcutis	Round cell	Excision	Died	Metastases present
28	Shoulder	Fibrosarcoma	Excision	Died	
29	Vulva	Myxosarcoma	Excision	Died	Aged 4 months from congenital heart disease. Metastases present
30	Parotid	Angiosarcoma	Excision	Recovered	Only short follow-up
31	Upper lip	Spindle cell	Excision plus radiation	Recovered	Follow-up 8 months

*Rearranged from Wells' publication to which the reader is referred for details.

All six patients upon whom amputations were performed recovered.

Excision was apparently sufficient for two patients, one of whom also received postoperative radiation.

One patient with liposarcoma of the leg was treated by radiation alone and was well after four years.

With exception of this last case, the congenital sarcomas of the extremities form a quite homogenous histologic group of a type that is generally con-

sidered radioresistant. However, there are not sufficient recent data available to determine definitely the role of radiotherapy in these lesions. Surgical treatment, on the other hand, has given uniformly good results and must be considered the treatment of choice, at least for the time being. Conceivably this attitude will require revision once results comparable to those obtained by surgery can be demonstrated by radiotherapists. Preoperative and postoperative radiation does not seem to add anything and, therefore, is not indicated.

It is difficult to select a standard operative procedure in these cases. None of the congenital sarcomas of the extremities has been found to spread to the lymph nodes. None has recurred locally; none has metastasized. The size and location of the tumor and the small terrain available in a newborn infant will make complete excision probably impractical in the majority of instances. Amputation on the other side has given uniformly good results. It should be done at the lowest possible level. In this way, one could justly hope for a permanent cure and at the same time the loss of limb kept at a minimum. In retrospect, the amputation as carried out in the present case, must be considered needlessly high.

Exarticulation would appear required only if amputation between tumor and joint is technically impossible.

2. Congenital sarcoma in locations other than the extremities has a much graver outlook. Only two out of nine patients are reported as cured. A third patient died when four months old from congenital heart disease at which time the tumor of the vulva had not recurred, but metastases were present. Histologically, these tumors are of greater variety. Local recurrences and metastases are more frequent. Complete surgical removal is impossible in many instances for technical reasons and incomplete removal has given poor results. It is possibly in this group that modern methods of radiation can be expected to improve the up-to-now disappointing picture.

SUMMARY

Congenital sarcoma is a rare lesion. A case of congenital sarcoma of the foot is reported. Analysis of all reported cases shows that congenital sarcoma of the extremities has a surprisingly good prognosis. Treatment is surgical. Amputation at the lowest possible level appears to be the most sensible approach. Radiation is no substitute for surgery but its possibilities cannot be fairly judged at this time. Congenital sarcoma in locations other than the extremities has a much graver prognosis. Surgical treatment is usually impractical or ineffective. Radiotherapy is considered preferable in this group whenever complete removal is impossible.

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CIRRHOSIS OF THE LIVER IN CHILDREN

A Clinical and Pathologic Study of Forty Cases

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INTRODUCTION

MANY papers have appeared during the past thirty years discussing the several types and characteristics of cirrhosis of the liver. However, there is only scattered information pertaining to such pathologic conditions in children. The available reports stress that the disease is uncommon in children. Most reports deal with a particular type or phase of cirrhosis and include only a few isolated, often unclassified, cases. No comprehensive report on the subject of juvenile cirrhosis is available. Nevertheless, as more data accumulate it appears that cirrhosis in children is not uncommon. Clinicians should be alert to recognize it and to understand its relationship to the various syndromes in which it may appear. Although juvenile cirrhosis morphologically does not often differ significantly from the disease in adults, there are certain features in regard to etiology, incidence, and pathogenesis that are more or less peculiar to children. For a discussion of hepatic cirrhosis in adults the reader is referred to the recent paper by Karsner.[1] The purpose of the present paper is to classify and correlate available data on the subject of juvenile cirrhosis and to report the cases studied at the St. Louis Children's Hospital. The peculiarities and problems which characterize the disease in children will be stressed.

Definition.—Cirrhosis is a term which should be applied only to the liver. In this paper cirrhosis applies to all sclerotic conditions of the liver in which there is destruction of the liver parenchyma with fibrous connective tissue replacement. The majority of patients whose cases are herein presented have had cirrhosis to the extent that the scarring could be recognized by gross examination. Any case in which fibrosis was questionable on examination of microscopic sections is excluded.

It is considered that when cirrhosis afflicts an individual under the age of 15 years, it can be considered juvenile cirrhosis. The upper limit in age for admission to The St. Louis Children's Hospital is 15 years, so this age limit was arbitrarily selected. The age of the oldest patient studied was 14 years.

Incidence.—Cirrhosis in children, especially the "biliary type" is a fairly common disease in India according to the reports of Ghose,[2] Radhakrishna Rao,[3] Prabhu,[4] and Chaudhuri.[5] In contrast, reported cases of juvenile cirrhosis in Europe and America are uncommon. The reason for this difference is not clear. Both a family tendency and multiple dietary deficiencies seem

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to be more consistently present in India than in temperate climates. Karsner[1] quotes De Josselin de Jong[6] as placing the incidence in children between 0.5 and 4.4 per cent of all cases of cirrhosis reported at the first conference of the International Society for Geographic Pathology in 1931. Passisni[7] cited six cases of cirrhosis among 160,000 children, but the autopsy rate is not specified. The combined figures of Menne and Johnston[8] and of Karsner[1] show an incidence of five cases of juvenile cirrhosis in 211 autopsied cases of cirrhosis of all ages. Nodular cirrhosis in children is especially rare. Further comments on its incidence will be made under a separate heading.

In the twenty-six years preceding 1947 there was a total of 82,866 admissions to the St. Louis Children's Hospital with 4,669 deaths and 2,441 autopsies. Among these there was a total of forty cases of cirrhosis, thirty-one confirmed by autopsy and nine proved by laparotomy with biopsy of the liver. There have been several additional cases diagnosed clinically as cirrhosis but without microscopic confirmation. They are not included in this report.

Familial Tendency.—The reports of Ghose,[2] Mackenzie,[9] and Jollye[10] indicate that a prominent familial tendency exists in those cases occurring in India and Mexico. Such a trait is also reported in America and in Britain by Ely,[11] Gunn,[12] Bridgeman and Robertson,[13] Yater and Saccardi,[14] and by Jameson and Savarese.[15] It is felt that some examples of cirrhosis may represent instances of incompatibility of blood group between mother and fetus (erythroblastosis fetalis) in which the family nature is well established and understood. Congenital biliary atresia, like other anomalies of development, shows a tendency to be familial. This is reported to be true of nodular cirrhosis also.

In the forty children herein reported all have come from separate families but a few of the histories suggest that more than one member of a family have been afflicted with the same disease. This is true especially in some of them classed under the heading of erythroblastosis fetalis.

Classification.—It is desirable in juvenile cirrhosis, as in all diseases, to make an etiological classification. Unfortunately this is not possible because of insufficient knowledge. In previous reports all cirrhosis in children is placed under a single classification of "juvenile cirrhosis" except for the few instances where a "biliary" or "nodular" type is distinguished. The following classification will be followed in the presentation of this series. It is a combination of the ones used by Moore,[16] and by Karsner[1] for adults, with the addition of erythroblastosis. It is adaptable to juvenile cases and includes most of the following types described in adults:

Obstructive biliary cirrhosis
Nodular (Laennec's, portal, atrophic, etc.) cirrhosis
Postnecrotic cirrhosis
Congestive ("cardiac") cirrhosis
Erythroblastosis fetalis
Hepatolenticular degeneration
Unclassified cirrhosis

The existence of other types of cirrhosis, e.g., syphilitic, pigmentary, lipoid, and zooparasitic is recognized, but these are not represented in our series.

OBSTRUCTIVE BILIARY CIRRHOSIS

Obstruction to the flow of bile from the hepatic cells into the duodenum may result from a variety of causes. The common cause in children is congenital atresia of the bile passages. Rare causes include stones in the common duct, enlarged lymph nodes about the major bile passages, inspissated viscid bile in the bile passages, and occlusion of the extrahepatic duct lumina by pressure or infiltration of tumor tissue. The site of the atresia is usually in the extrahepatic bile passages according to Stolkind,[17] Holmes,[18] and Ladd.[19] Authentic examples where the obstruction is located in the intrahepatic portions of the ducts are recorded by McClendon and Graham,[20] and by Parsons and Hickmans.[21]

The best explanation for congenital anomalies of the bile ducts is that which attributes them to incomplete or improper embryonic development. The factors that influence or control embryonic development are not understood. It is noteworthy that anomalies of the bile passages are sometimes associated with other anomalies, especially of the heart.[22] A familial tendency is sometimes shown.[23, 24] The reported incidence of congenital atresia of the biliary system is not large. Motsay and May[25] state that up to 1945 only about 200 cases were described in the American literature. Donovan[26] reported an incidence of sixteen cases in 21,000 admissions at the New York Babies' Hospital over a ten-year period. In 2,441 autopsies at the St. Louis Children's Hospital in the last twenty-six years only five patients with demonstrable atresia of the bile passages other than the gall bladder or cystic duct are recorded. In one (Case 7, Table I) the obstruction was due to fibrosis of aberrant pancreatic tissue in the duodenal wall. Two additional children had laparotomies with liver biopsy during the same period. These eight cases are included in this report. Other instances diagnosed clinically and still others where laparotomy was performed but without liver biopsy are not included in this study.

It is important to remember that all patients with congenital anomalies of the bile ducts that obstruct the flow of bile from the liver develop cirrhosis if they live any appreciable length of time. Chesterman[27] in his article on congenital bile duct atresia states, "The liver is invariably involved with chronic obstructive cirrhosis unless the cystic duct or the gallbladder only are atretic." It is also important to stress that the ultimate termination of all unoperated patients with complete obstruction of the ducts is death early in life. Most patients die before eight months of age although the one reported by Finlayson[28] lived three years and three months. This seems to be a record. Our patient that lived longest with complete obstruction of the major bile ducts died at the age of 30 months. One in this series had complete obstruction of the common duct but an anomalous accessory duct directly from the liver to the ampulla of the gall bladder. The lumen of this accessory duct was much

TABLE I. SUMMARY OF FINDINGS IN OBSTRUCTIVE BILIARY CIRRHOSIS

	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5	CASE 6	CASE 7	CASE 8
Age at onset of jaundice	10 days	1 day	9 days	14 mo.	3½ mo.	2 to 3 week	5 years	7 days
Age when first seen	5 mo.	8½ mo.	7 mo.	2½ yr.	5½ mo.	6 week	5¾ yr.	4 mo.
Age at death or biopsy	5 mo.	9 mo.	7 mo.[1]	2¾ yr.[2]	4¾ yr.[3]	2 mo.	5¾ yr.	5 mo.
Hepatomegaly	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Splenomegaly	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Ascites, in cubic centimeters if known	200[4]	100[4]	No	1,600[5]	1,600[5]	No	Slight	200
Prominent abdominal veins	Yes	Yes	Yes	No	Yes	No	Yes	No
Purpuric tendency	Yes	No	No	No	Yes	Yes	Yes	Yes
Hemorrhage in gastrointestinal tract[6]	No	Yes	No	No	No	No	Yes	Yes
Malnutrition	Yes	Yes	Yes	Yes	Yes	No	No	No
Respiratory infections	Yes	Yes	Yes	No	Yes	No	No	Yes
Hernia	Umbilical and inguinal	No	No	Umbilical	No	No	No	No
Hemoglobin in grams per 100 c.c.	8.0	7.6[6]	10.0	7.4[7]	5.8[7]		5.8[7]	7.8[6, 7]
Leucocyte count	16,500	25,000[7]	14,800[7]	11,350[7]	25,900[7]	12,700	74,000[7]	28,350[7]
Clotting time in minutes	-	-	3½	5	-	More than 30[7]	4½	2
Bleeding time in minutes	-	-	3	2	3	Prolonged	2½	4¾
Prothrombin time	-	Prolonged	-	Prolonged	Normal	-	-	Normal
Serum albumin in grams per 100 c.c.	-	4.6	-	3.0	2.50[7]	-	3.09	3.16
Serum globulin in grams per 100 c.c.	-	2.85	-	3.6	4.20[7]	-	4.57	2.34
Serum total protein	-	7.45	6.05	6.6[7]	6.70[7]	-	7.03[7]	5.50
Icterus index	118	150[7]	92	110[7]	120[7]	-	55	160
Van den Bergh	Direct	-	-	Direct	Direct	Direct	Direct and indirect	-
Urine bilirubin	Present	Present	-	Present	Present	Present	Present	Present
Urine urobilinogen	-	Absent	-	-	Absent	Absent	-	-
Clay-colored stools	Present	Present	Present	Present	Intermittent	Present	Present	Present

[1]Date and circumstances of death not known.
[2]Died at 3 years, 10 months, at home.
[3]Died at 4 years, 8 months, at Homer G. Phillips Hospital.
[4]At autopsy.
[5]At laparotomy.
[6]Nucleated red blood cells found in peripheral blood.
[7]Where more than one determination is reported, the most extreme value is given.
Serologic test for syphilis was negative in all cases.

smaller than the usual common duct. This patient lived with partial obstruction to be 4 years, 9 months old.

In obstructive biliary cirrhosis the etiology and the pathogenesis are well understood. The morphologic findings are quite uniform. This form of cirrhosis has been studied and reproduced experimentally. For the surgical aspects of this disease and the pathology other than the cirrhosis the reader is referred to the articles by Ladd,[19] Amberg,[22] Behrend,[29] and to Ladd and Gross.[30]

The clinical findings in obstructive biliary cirrhosis include a progressive jaundice that begins in the congenital cases a few days after birth. There are clay-colored stools, dark urine, an enlarged and palpable liver, and a moderate splenomegaly. Ascites of significant degree is not uncommon, and the superficial abdominal veins frequently are prominent. Nutrition usually is good. There is an abnormal susceptibility to respiratory infections. The laboratory findings are those of complete obstructive jaundice, viz.; a high icterus index, excessive bile in the urine, a direct Van den Bergh reaction, decreased liver function late in the disease as indicated by special tests, and, most important, the presence in the urine of no more than traces of urobilinogen, or none at all.

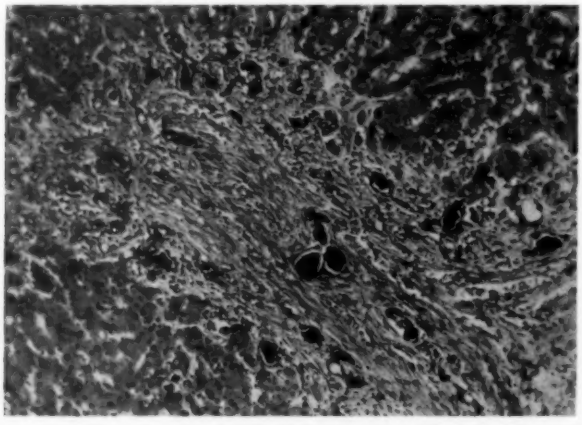

Fig. 1.—R. W. Obstructive cirrhosis, showing great increase in periportal connective tissue with inflammatory infiltration; bile pigment chokes the ducts and is taken up by Kupffer cells. (Case 9, Table I.) (×100.)

The differential diagnosis includes icterus neonatorum, erythroblastosis fetalis, jaundice due to sepsis and to congenital syphilis. Except for icterus neonatorum the jaundice of these conditions may be the complete obstructive type for a transient period.

The gross pathologic findings, in addition to the assorted malformations of the bile ducts, include a generalized icterus of the tissues and a large nodular liver with variable amounts of scarring. The microscopic picture is that

of an interlobular fibrosis, bile stasis, and, to a limited degree, the presence of lymphocytes and monocytes. The architecture of the liver may be somewhat more distorted in children than in obstructive cirrhosis in adults. Table I shows the clinical and laboratory data on eight cases of obstructive biliary cirrhosis. A characteristic section showing the usual microscopic features is shown in Fig. 1.

DIFFUSE NODULAR CIRRHOSIS

Diffuse nodular cirrhosis, also known as Laennec's, portal, atrophic and alcoholic cirrhosis, and hobnail liver, is a classification based purely on morphologic findings. This is not ideal. Improvement awaits a better knowledge of its etiology and pathogenesis. The pathologic anatomy does not differ in children from adults. Presumably the same etiologic factors (alcohol, dietary deficiency, infection, hepatotoxic agents, etc.) hypothesized as playing a role in the production of nodular cirrhosis in adults, may be the factors responsible for the production of juvenile nodular cirrhosis. Alcohol must be a less common casual agent.[31] Several writers[12, 13, 15, 31, 32] state that there is a tendency for the disease to occur in families. None of the cases herein presented show such a trait. The incidence of the disease in children is less than in adults. Bridgeman and Robertson[13] in 1932 reported the fourteenth American case of nonalcoholic nodular cirrhosis. To our knowledge none have been reported since. There are also about fifteen cases reported of alcoholic nodular cirrhosis. In the past twenty-six years there have been eleven cases at the St. Louis Children's Hospital which by biopsy or at autopsy have presented the characteristic tawny, firm, grossly nodular liver, splenomegaly, and portal varices. The microscopic findings are those of an extensive perilobular fibrosis, focal regeneration of parenchymal cells, and chronic inflammatory cell infiltration of the scar tissue. The history in some cases suggests possible casual agents. They may be only coincidental, however, and unrelated to the fibrosis of the liver. Selected case reports are presented below, the numbers corresponding to those in Table II.

Case 1.—C. B., aged 9, a white boy, entered the hospital on June 13, 1923, having been well until the appearance of anorexia and progressive weight loss eight months before. The abdomen had gradually enlarged.

The family and past histories were unrevealing save that at the age of 4 years the child had been very ill for a month with "trench fever." The father had died from the same disease.

At the time of admission the child was extremely emaciated with a huge, protruding abdomen that was covered with dilated superficial veins. There was evidence of ascites. After paracentesis the spleen was found to be greatly enlarged. The liver also was enlarged, hard, and nodular. Hemorrhoids were prominent. These findings confirmed by an exploratory laparotomy, together with gross glycosuria and hyperglycemia, led to the diagnosis of diabetes mellitus and cirrhosis of the liver. A section of the liver is shown in Fig. 2.

Case 3.—W. H., a Negro boy aged 9 years, was the only child of healthy parents. The mother's second pregnancy resulted in a miscarriage at two

TABLE II. SUMMARY OF FINDINGS IN NODULAR CIRRHOSIS

	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5	CASE 6	CASE 7	CASE 8	CASE 9	CASE 10	CASE 11
Age at onset of symptoms	8 yr.‡	17 mo.‡	8½ yr.	5 yr.	9 yr.	8 yr.	13 yr.‡	3½ yr.	Infancy‡ ‡		3 mo.‡
Age when first seen	9 yr.	17 mo.	9 yr.[1]	5½ yr.	9½ yr.	8 yr.	13 yr.	7 yr.	6½ yr.	11 yr.	3 mo.
Age at death* or biopsy†	9 yr.*	9 yr.*	9 yr.† 10 yr.*	6¾ yr.† 7½ yr.*	9½ yr.*	8 yr.*	13 yr.*[2]	8 yr.†[3]	6½ yr.†[4]	14½ yr.*	4 mo.*
Hepatomegaly	Present[5]	Present	Present	Present[5]	Present	Present	Present	Present	Present	Absent	Present
Splenomegaly	Present	Present	Present	Present[6]	Present	Present	Present	Present	Present	Present	Absent
Ascites, in cubic centimeters, if known[7]	5,000[8]	600[9]	70	700[9]	400[9]	2,000[9]	None	None	None	None	300[9]
Jaundice	Absent	Absent	Present	Present	Present	Present	Present	Present	Absent	Present	Absent
Hemorrhage in gastrointestinal tract[10]	Present	Present	Present	Present	Present	Present	Absent	Absent	Absent	Present	Absent
Hemorrhagic tendency elsewhere	Absent	Present	Present	Present	Present	Present	Present	Absent	Absent	Present	Absent
Prominent abdominal veins	Present	Absent	Absent	Absent	Absent	Present	Questionable	Absent	Present	Absent	Absent
Malnutrition	Present	Present	Absent	Absent	Present	Present	Absent	Absent	Present	Absent	Present
Anorexia	Absent	Present	Absent	Absent	Present	Present	Present	Absent	Present	Absent	Present
Respiratory infections	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Drowsiness	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No
Hemoglobin in gram per 100 c.c.	–	–	7.3[12]	6.5[12]	9.4[12]	11.0	7.9	10.5	9.0	8.0	–[13]
Leucocytes[12]	9,200	14,100	29,000	29,600	5,700	14,400	3,100 25,100	1,300 42,700	14,100	3,000	34,500
Clotting time in minutes	–	–	–	20[12]	8	13	2	12[12]	–	3½	–
Bleeding time in minutes	–	–	–	9[12]	5′ 50″	6	4	4	11	6½	–
Prothrombin time	–	–	–	–	Prolonged	Prolonged	–	–	–	Normal	–
Serum albumin in gram per 100 c.c.	–	–	–	–	1.92	5.20	–	–	–	3.4	–
Serum globulin in gram per 100 c.c.	–	–	–	–	6.79	1.95	–	–	–	3.8	–
Serum total protein	–	–	–	9.90	8.71	7.16	–	–	–	7.2	4.30
Icterus index	–	–	270[12]	75[12]	78	240[12]	15[12]	3	–	25[12]	–
Van den Bergh	–	–	Immediate direct, indirect	–	Immediate direct	–	–	Negative	–	Immediate direct	–
Urine bilirubin	–	–	Present	Present	Present	Present	–	–	–	Slight	–
Urine urobilinogen	–	–	Present	–	Present	Present	–	–	–	–	–
Clay-colored stools	Absent	Absent	Present[14]	Absent	Present[14]	Present[14]	Absent	Absent	Absent	Present	Absent
Clinical diagnosis made or suggested	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	No

[1]Had had three previous admissions for herniorrhaphy, pneumonia, and tuberculosis, but no evidence of cirrhosis was then reported.
[2]Died at age 22 with advanced cirrhosis.
[3]Living and well when last seen in 1940, aged 9 years.
[4]Living and well when last seen in 1945, aged 6½ years.
[5]Liver regressed in size subsequently.
[6]Spleen regressed in size subsequently.
[7]Maximum value given.
[8]At laparotomy.
[9]At autopsy.
[10]Some, but not all of such hemorrhage represents true bleeding tendency rather than ruptured varices.
[12]Where several values are reported, the most abnormal is given.
[13]RBC, 4.23 million.
[14]Stool contained bile at times.
*At death.
†At biopsy.

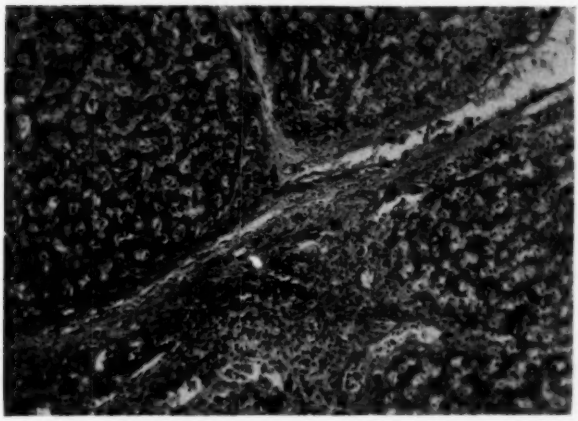

Fig. 2.—C. B. Nodular cirrhosis, showing increase in periportal connective tissue, round cell infiltration, dilatation of the sinusoids, and sharp demarcation of the lobules. (×100.)

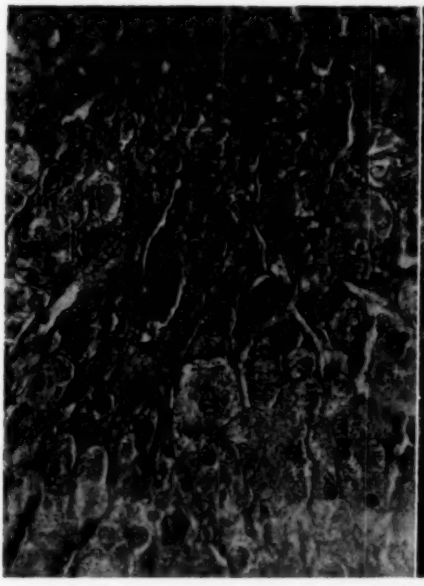

Fig. 3. Fig. 4.

Fig. 3.—W. H. Biopsy sixteen months before death, showing periportal blood extravasation and the swollen, coarsely granular cytoplasm of the parenchymal cells. No evidence of cirrhosis. (Mallory stain, ×100.)

Fig. 4.—W. H. Autopsy showing islands of liver cells surrounded by interlacing strands and large areas of fibrosis with great distortion of architecture. The fibrous tissue is relatively cellular and shows round cell infiltration. Sinusoids are dilated and there is cloudy swelling of liver cells but no frank necrosis. (See Fig. 3, sixteen months earlier.) (×100.)

months. The family history otherwise is unrevealing. He was first admitted in 1927 for bilateral hernioplasties. Pneumonia from which he recovered complicated the postoperative course. He again had pneumonia in 1930 and in 1931. Soon after, a diagnosis of pulmonary tuberculosis was made. After treatment for two and one-half years in a sanatorium he was discharged as having an arrested case of tuberculosis. Liver disease up until this time was not diagnosed. In 1934, at the age of 9 years, he was readmitted to Children's Hospital. Several months after discharge from the sanatorium he had developed gradually a progressive jaundice. A week before admission he had become listless, sluggish, and his legs ached. The day before admission he experienced visual disturbances, nausea and vomiting, and headache. His stools were flecked with blood.

The patient was fairly well nourished, markedly jaundiced, and had a mild rhinopharyngitis with a low-grade fever. His liver was palpable but not considered enlarged. The spleen was very large. Hematologic findings were within normal limits safe for leucocytosis. His tuberculin reaction was 4 plus, and serology was negative.

Laparotomy revealed a spleen twice the normal size and a grossly smooth but firm liver. A biopsy of the liver was taken (see Fig. 3).

Sixteen months later he was readmitted. Jaundice had persisted, visual disturbances which had cleared returned, and he developed a marked tremor of the hands. On several occasions he had nosebleed. Mental confusion was marked. Physical examination revealed a large, hard liver and a prominent splenomegaly. Ascites was present. Anemia was marked. Laparotomy revealed a nodular cirrhotic liver and a huge spleen. The contemplated splenectomy was abandoned because of uncontrollable hemorrhage. The patient died a few hours later.

Autopsy disclosed an advanced nodular cirrhosis of a 1,100 gram liver. The spleen weighed 700 grams. Sections of the spleen showed prominent sickling of the red blood cells. For the microscopic appearance of the liver see Fig. 4.

CASE 4.—S. S., a girl, aged 5, was admitted to the hospital with a diagnosis of scarlet fever and a past history of repeated epistaxes. An incidental finding was that of a marked splenomegaly. The day after discharge she had another severe nosebleed and was readmitted for a day.

Nine months later she was again readmitted. Her complaints were anorexia of one year's duration, repeated epistaxes, and epigastric pain with vomiting. Epistaxes had been frequent for a month. There was generalized lymphadenopathy, persistent low-grade fever, and mild icterus. The liver was not felt. The spleen extended only 3 fingerbreadths below the costal margin. The patient was discharged unimproved after two weeks. She did poorly from that time on; she was hospitalized on two other occasions; death resulted from pneumonococcus pneumonia in December, 1939. On the final admission she had clinical ascites confirmed by autopsy. Her liver, which was of average size, was nodular and grossly cirrhotic. Autopsy section (Fig. 6) of the liver showed marked advancement of the cirrhotic process previously seen in the biopsy section in Fig. 5.

Discussion.—The etiology of the cirrhosis in these cases of nodular cirrhosis is still obscure. It is true that several of the patients had acute infectious disease (trench fever, pneumonia, tuberculosis, influenza, etc.) prior to the onset of clinical liver disease. Whether these infections were specific or

remote causes of liver damage is problematical. The likelihood that they were merely coincidental is great. In several cases dietary deficiency may have been a factor. Case 2 is known to have had rickets years before the clinical signs of cirrhosis appeared. The evidence that a deficient diet played a role is not at all convincing. The relationship of tuberculosis and diabetes mellitus to cirrhosis where both diseases existed is probably only coincidental. Case 2 also had congenital heart disease but only terminally was there any evidence of cardiac decompensation, so it is believed the extensive cirrhosis seen at autopsy was not the result of chronic passive congestion. No statement relative to alcohol ingestion by these children is included in the histories. The possibility of erythroblastosis fetalis being the initial underlying cause of

Fig. 5.

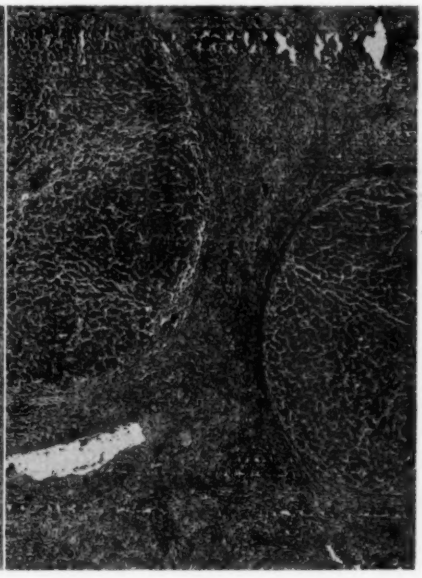

Fig. 6.

Fig. 5.—S. S. Biopsy, nodular cirrhosis, showing diffuse portal scarring with moderate lymphocytic infiltration. (×60.)

Fig. 6.—S. S. Autopsy, showing great increase in fibrosis by comparison with Fig. 5 nine and one-half months earlier. Hepatic cells embedded in the connective tissue are rare, but there are many bile ducts and small collections of leucocytes. (Masson stain, ×60.)

the disease in some of these patients cannot be ignored. Three patients have family histories of miscarriages. There are no available Rh studies to confirm a suspicion of Rh incompatibility in any of the eleven cases. It is worth noting that sickle cell anemia and cirrhosis are sometimes associated. Such was the case in one of these eleven patients. The mechanism of liver damage might be similar to that postulated for erythroblastosis fetalis. The surgery could occur during a sickle cell crisis.

Most of these patients presented the clinical picture that was once called "Banti's disease." Some of the less advanced cases, however, did not have anemia and leucopenia. Ascites was present in seven patients. Jaundice was absent in three cases, including one of the most severe. The very large spleen found in all but one was in most instances the result of portal hypertension which results from obstruction of the portal blood flow through the cirrhotic liver. The details of this mechanism are explained by Moore.[16] Case 2 is known to have had a large spleen seven years before she developed further clinical evidence of cirrhosis. Case 8 had bleeding tendencies and a splenomegaly three years before becoming ill. It seems unlikely that cirrhosis per se so early in the disease caused hypertension and splenomegaly.

It seems logical to conclude from this study as well as from the findings of other authors that nodular cirrhosis may be an advanced stage of some process that was precipitated by various etiologic agents. If more were known of the pathogenesis these patients might belong under the classification of erythroblastosis fetalis or postnecrotic cirrhosis.

Diagnosis.—A history of gradual, usually painless swelling or enlargement of the abdomen, often associated with swelling of the lower extremities, is the most common subjective symptom. There is often a long story of anorexia, weakness, and gradual weight loss. Attacks of jaundice in the past or beginning with the onset of the present illness are quite common. Vague abdominal pain, discomfort, and distress may be present in these patients. Both drowsiness and irritability frequently are mentioned. A history of bleeding from the nose, esophageal varices, or hemorrhoids is consistent enough to be helpful.

All of these patients save one had a splenomegaly. All but one had a palpable hard liver. Ascites is a common finding and often is associated with dependent edema. Prominent superficial veins occur but the so-called venous spiders have not been a finding of any frequency in these or other reported cases in children. Poor nutrition and susceptibility to infections are consistent findings. The age of onset in our group has varied from less than one year to 13 years.

In those children where the liver damage is extensive enough, liver function tests will show evidence of decreased liver function. Low total proteins with increase in the globulin fraction and decrease in albumin is a common finding where there is ascites or dependent edema.

X-ray studies may be utilized to demonstrate esophageal varices and an enlarged spleen also may be shown.

Biopsy of the liver is the only method whereby an accurate diagnosis can be made. It should be resorted to unless there are strong contraindications. Laparotomy is the ideal method of securing a liver specimen. It is safe, an adequate specimen can be obtained, and the liver can be inspected grossly. However, Hoffbauer, Evans, and Watson[33] strongly recommend needle biopsy. They feel it is indicated if liver function tests prove equivocal and laparotomy seems inadvisable.

ERYTHROBLASTOSIS FETALIS

Several authors have reported examples of juvenile cirrhosis in which there was a history of severe neonatal jaundice.[34-38] Many of them may well have been the one clinical form of erythroblastosis known as icterus gravis. Hawksley and Lightwood,[39] in 1934, suggested and gave evidence that some cases of juvenile cirrhosis are associated with erythroblastosis. Poynton and Wyllie[40] point out that in those infants with icterus gravis who do not die in the first few days after birth, the microscopic post-mortem details are strongly suggestive of early biliary cirrhosis. Braid and Ebbs,[41] in 1927, and Webster,[42] in 1938, reported instances of cirrhosis in children that followed neonatal icterus gravis. Henderson[43] has recently reported four stillborn infants who, in addition to having the findings of erythroblastosis, also had marked hepatic cirrhosis. The incidence of erythroblastosis is estimated to be one per 200 births in American infants. The incidence of cirrhosis following erythroblastosis must be rare, as only a very few cases are reported in the literature.

From our studies we have arrived at the conclusion that many cases of juvenile cirrhosis in early adulthood may be a part of or the end result of fetal erythroblastosis. Recent knowledge about Rh factors and anti-Rh agglutinins in the blood[44-46] makes it possible to diagnose the less typical forms of the disease (forms without anemia, without erythroblastosis, with complete obstructive jaundice, and with only mild abortive manifestations). The pathogenesis of erythroblastosis as given by Davidsohn[46a] postulates that extramedullary hematopoiesis and anoxemia result in liver damage. In examining the slides on our cases we have been impressed with the fact that the distribution of the fibrosis is very similar to that of the extramedullary hemopoietic centers and that fibrosis about the existing centers, when present, is very noticeable.

TABLE III. SUMMARY OF FINDINGS IN ERYTHROBLASTOSIS FETALIS

	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5
Familial incidence	Absent	Present	?	Absent	Absent
Life span	2 mo.	2 days	1 day	9 weeks	10 weeks
Age at onset of jaundice	3 days	1 day	?	1 mo.	1 day
Purpuric tendency	Present	Present	Present	?	Absent
Hepatomegaly	Present	Present	Present	Present	Present
Splenomegaly	Present	Present	Present	Present	Present
Edema	Absent	Slight	?	Absent	Absent
Hemoglobin in gram per 100 c.c.	9.0	11.3	17.8	9.5	15.6
Leucocytes	52,000	64,400	49,600	17,800	94,200*
Leucemoid blood picture	Present	Present	Present	Absent	Present
Nucleated R.B.C. in circulation, per 100 W.B.C.	27	4	10	Present	5
Icterus index	115	150	-	65	-
Blood Kline	Negative	Negative	Negative	Negative	Negative
Mother Rh-negative, father and child positive	Yes	Yes	Not known	Not known	No†
Extramedullary hematopoiesis	Present	Present	Present	Present	Absent
Biliary stasis	Present	Present	Present	Present	Present
Hemosiderosis	Present	Present	Present	Absent	Present
Cirrhosis	Marked	Slight	Slight	Marked	Moderate

*This patient had bilateral otitis media, diarrhea, and a subcutaneous abscess.
†Rh data may be inaccurate.

Five of the cases studied here are classified under the heading of erythroblastosis fetalis. In two instances the clinical, laboratory, and pathologic data are conclusive. This includes the Rh information. Unfortunately Rh data is not available on two children but on clinical and pathologic grounds the diagnosis is quite certain. The fifth case probably falls into that group of patients with erythroblastosis where the Rh factor is not in question. The Rh typing of this patient and his parents was done early and may be incorrect. Several other cases classified elsewhere may have been erythroblastosis but no Rh data is available and the clinical findings are not complete enough to warrant placing them under this heading. Table III summarizes the findings of these five children. Sections of the liver are shown in Figs. 7 and 8.

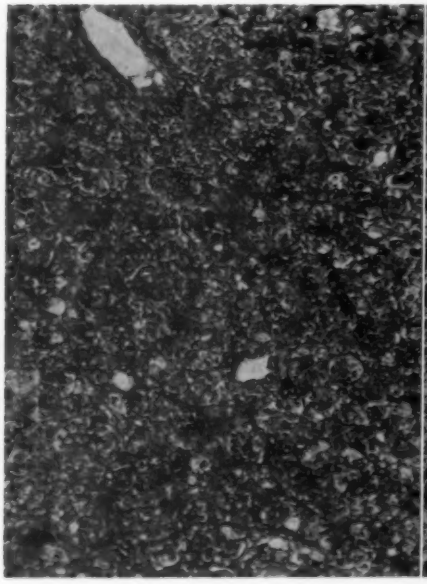

Fig. 7.

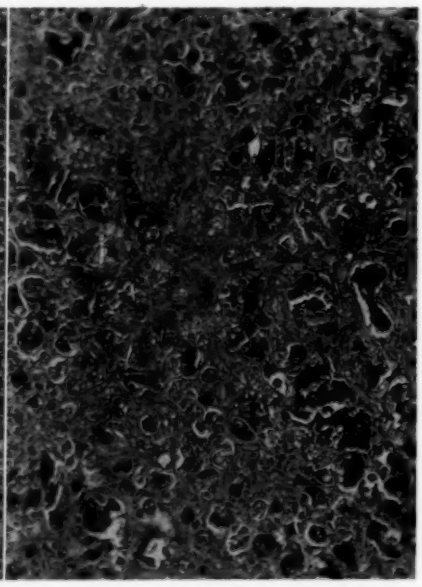

Fig. 8.

Fig. 7.—J. E. Erythroblastosis, biopsy nine days before death showing destruction of architecture, large, vacuolated, foamy, liver cells, diffuse hemorrhage, and old scar tissue with round cell infiltration. Regeneration of liver cells in some areas indicates actively progressive cirrhosis. (Case 1, Table III). (Masson stain, ×100.)

Fig. 8.—J. E. Autopsy. Note increase in diffuse fibrosis and complete destruction of liver architecture. Generalized hemosiderosis. (Masson stain, ×100.)

The clinical findings in erythroblastosis fetalis include jaundice, edema or anemia. Such manifestations may occur at birth or soon thereafter. These manifestations vary with the gravity of the disease. Hepatomegaly and splenomegaly are prominent. Hemorrhagic manifestations may be present. Although some cases are rapidly fatal, most patients recover. Some of those who recover probably retain varying degrees of cirrhosis of the liver as

residuals. The presence of many nucleated red blood cells is the rule but is not universal. A leucemoid blood picture is usual. A high icteric index is present. Low fractional proteins are often observed, and the prothrombin time frequently is abnormal. Of prime importance in establishing a diagnosis are the Rh data, which in 90 per cent of the patients will show an Rh-positive father and child but an Rh-negative mother. Agglutination antibodies in the maternal serum are conclusive evidence when they can be demonstrated.

A large spleen and liver with extramedullary hemopoiesis are usual but not universal findings at autopsy. Evidence of parenchymal damage to the liver usually can be demonstrated with hepatic necrosis and biliary stasis. Hemosiderosis usually is conspicuous. Whether cirrhosis occurs probably depends upon the extent and nature of the liver damage and whether or not the adverse situation of the liver is severe enough to prevent repair in the form of fibrosis. It would seem that the extremely severe cases would show progressive irreversible damage to the liver while the very mild cases would have no demonstrable changes. Between these two extremes some would show damage, destruction, and repair with some degree of fibrosis as the end result. In these cases the diffuse nature of the fibrosis, in contrast to the nodular distribution seen in other forms, has been a striking and consistent feature.

CONGESTIVE CIRRHOSIS

Congestive or cardiac cirrhosis is an entity quite different in clinical context and in pathologic picture from the other forms of cirrhosis. Some investigators feel that it should not be classified as true cirrhosis because it does not, to their satisfaction, meet all the requirements of the definition of cirrhosis by Moon:[47] "Cirrhosis of the liver occurs in several forms, is a progressive chronic inflammation, diffuse in extent, accompanied by fibrosis, retrogressive changes in the parenchymal cells and changes of remaining cells in the direction of proliferation." Regeneration is the feature that is usually hard to demonstrate in cirrhosis due to chronic passive congestion. Koletsky and Barnabee[48] studied seventy-five patients with heart disease in which prolonged single or multiple episodes of congestive failure had occurred. These they divided into three groups, of which the third showed not only atrophy, necrosis, and condensation of reticulum but "true cirrhosis," which included, with the other criteria, regeneration of hepatic tissue. They state: "The patchy nature of the fibrosis, and the intervening regions of central degeneration and condensation of reticulum made the picture differ considerably from that usually seen in advanced portal cirrhosis." They emphasize the distinction between single and multiple episode cases, and advance an ingenious concept of pathogenesis. It is presumed that gradual passive congestion leads to atrophy, rapid or terminal congestion, and to necrosis. In the intervals between episodes of gradual congestion recovery takes place with condensation and thickening of reticulum, but only if necrosis has spared enough of the lobule for healthy cells to replace the destroyed ones. Congestion severe enough to necrotize will not permit adenomatous regeneration. It must be realized that a special combination of circumstances must exist before a given cardiac patient will develop

TABLE IV. SUMMARY OF FINDINGS IN CONGESTIVE CIRRHOSIS

CASE	AGE FIRST SEEN	AGE AT DEATH	DURATION OF HEART DISEASE	EARLIEST EPISODE OF FAILURE[1]	HEPATOMEGALY[1]	SPLENOMEGALY[1]	CLINICAL ASCITES[1]	JAUNDICE[1]	INFECTIONS[1]	PRINCIPAL CLINICAL AND PATHOLOGICAL DIAGNOSES
1	6¾ yr.[2]	15 yr.	4 yr.	4 yr.	Palpable on first admission; not again until 5 yr. later; tender, firm; range 1-4 fb.	4 yr., faintly palpable; 7 mo., 1 fb.	4 mo.	3 mo.	Pharyngitis, 4 yr.; bronchitis, 3 yr., 2 yr.; pneumococcal pneumonia, 2 mo.	Rheumatic heart disease with congestive failure; chorea; chronic endocarditis of all four valves with advanced mitral stenosis; fibrous pericarditis; lobar pneumonia; chronic passive congestion of liver with fibrosis and fatty degeneration.
2	12 yr.	14 yr.	Congenital	2 yr.	2 yr., to umbilicus, pulsating; at least one regression.	2 yr., just palpable; 2 weeks, not felt	2 weeks, questionable.	No	2 yr., pneumonitis; 2½ mo., pleurisy.	Patent interventricular septum and foramen ovale, patent ductus arteriosus, infarcts of lung and myocardium, chronic passive congestion of lungs and liver, cirrhosis.
3	7½ yr.	11 yr.	3½ yr.	3½ yr.	3 yr., 1-2 fb.; thereafter variable 0-4 fb.	No	3 mo.	No	3½ yr., rheumatic fever.	Chonic rheumatic endocarditis involving mitral and tricuspid valves, fibrous pericarditis, chronic passive congestion of lungs, liver, spleen, and kidneys, cirrhosis, cholelithiasis.

4	7 yr.	9 yr.	Congenital	6 yr.	3 yr., 10 cm. below costal margin; variable thereafter.	3 yr., 1 fb.; palpation thereafter obscured by ascites.	2 yr., marked, progressive.	No	1 yr., erysipeloid; 1 yr., diarrhea; 4 weeks diarrhea; 2 yr., chronic otitis media	Congenital pulmonic valve stenosis, chronic passive congestion of liver and spleen, cirrhosis.
5	17 days	4 weeks	Congenital	9 days[1]	17 days, 2 fb., firm.	17 days, 2 fb., firm.	150 c.c.	7 days, slight; 2 days, intense.	No	Saccular dilatation of patent ductus arteriosus; hypertrophy and dilatation of heart; thrombi in thebesian veins and in right and left ventricles, in abdominal aorta and several mesenteric branches; chronic passive congestion of liver, with marked loss of hepatic parenchyma, fibrosis, and calcification.
6	6½ mo.	7 mo.	-	-	2 weeks, hard, smooth, scalloped, 3-4 fb.	2 weeks, "enlarged."	2 wk. or more.	2 weeks, slight; terminally increased.	6 weeks, bronchitis.	Thrombophlebitis of hepatic vein near vena cava; cirrhosis; acute ulcerative colitis; chronic passive congestion of spleen and liver.

fb Represents "fingerbreadths below the costal margin."
[1]Time given represents interval before death.
[2]Patient admitted with chorea, the first clinical evidence of cardiac disease, compensated, was aged 11 years.

cirrhosis. Decompensation must be present intermittently to produce focal liver damage from chronic passive congestion and the interval repair by fibrosis of the damaged areas. Both clinically and pathologically, congestive cirrhosis resembles little the other forms of cirrhosis. Chronic passive congestion is the predominant features, as is brought out by Lambert and Allison.[50] Of course, heart disease per se with the common findings of chronic decompensation are the outstanding clinical features.

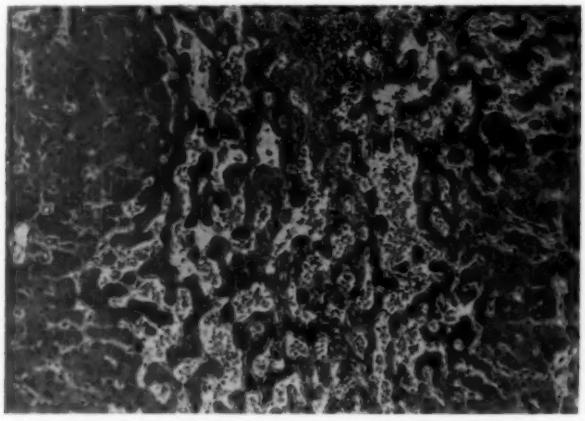

Fig. 9.—E. W. Cardiac cirrhosis, showing dilatation of sinusoids in the region of the central vein, with atrophy of liver cells and some increase in fibrous tissue and reverse lobulation. (Case 3, Table IV.) (Masson stain, ×100.)

On the status of cardiac cirrhosis as a clinical diagnosis it is worth while to quote Katzin, Waller, and Blumgart.[51] They studied 2,000 consecutive autopsies which included 286 cases of chronic passive congestion:

"By the evidence obtained the meaning of the term 'cardiac cirrhosis' is clarified. Cardiac cirrhosis (meaning morphologic increase in connective tissue in liver consequent to congestive failure) is present in the majority of patients who have suffered from even mild congestive failure for 9 months or more; the fibrosis may be central or portal or both. Clinical cardiac cirrhosis, on the other hand (meaning extreme fibrosis which clearly results from chronic passive congestion and which causes evidence of portal obstruction), does occur, but is rare. Of the 286 cases of failure, there were only 15 in which marked but not necessarily predominant ascites required abdominal paracentesis. The clinical diagnosis of cardiac cirrhosis can be made only rarely, since it must be based on the finding of preponderant ascites, a small liver in spite of elevation of the venous pressure and particularly the presence of a palpable spleen. Not infrequently, however, the liver may be enlarged."[51]

Congestive cirrhosis may be viewed as the end result of prolonged but intermittent congestion of the liver. In children the usual cause is cardiac decompensation. However, one child whose case is presented here (Table IV) developed chronic passive congestion and cirrhosis of the liver because of an

obliterating endophlebitis of the hepatic vein with partial obstruction. Similar cases are reported in adults by Rigdon[54] and Hutchison and Simpson.[55] Zimmermann and Hillsman[53] were able to produce fibrosis in the liver experimentally by gradual occlusion of the vena cava. The clinical effects of cirrhosis on a congestive basis are likely to be overshadowed by the primary cause of the congestion in heart failure, but not so in patients where the obstruction to venous return is in the hepatic vein. The principal microscopic characteristic is an increase in central rather than in periportal fibrous tissue and necrosis of the liver parenchyma. Associated evidence of central chronic passive congestion (nutmeg liver) is striking. The only feature that seems to differ in children from the condition in adults is that the liver is more likely to be enlarged than shrunken.

Clinical and pathologic findings in this series of six cases are summarized in Table IV, and Fig. 9 shows a representative microscopic section.

POSTNECROTIC CIRRHOSIS

Postnecrotic cirrhosis is sometimes called coarsely nodular cirrhosis and healed acute or subacute yellow atrophy of the liver. It is a classification based principally on morphology, although sometimes the destructive or "toxic" agent can be identified. When it is identified the affection would be better classified under an etiologic category. This type of cirrhosis has been reproduced experimentally using different agents. Such experimental studies have contributed much to our understanding of the several diseases associated with cirrhosis. Among the common agents which are known to produce extensive liver necrosis which may result in subsequent scarring are chloroform, Salvarsan, cinchophen, carbon tetrachloride, and the various sulfonamides (Moore[16]). The characteristic findings are a small liver with irregular liver nodules, interspersed with bands of scar tissue. The findings differ from those of nodular cirrhosis only in that the nodularity is much less regular and the parenchymal nodules are less uniform. Both gross and microscopic findings vary from case to case depending on the amount, the nature, and the time prior to exposure of the hepatotoxic agent. We agree with Karsner[1] that in many of the less classical cases one cannot distinguish between the two forms. The identification from the history of the etiological agent is desirable, when possible, to make the diagnosis more complete and certain.

Karsner[1] found the incidence of the postnecrotic type in his study to be 10 per cent (all ages), and he quotes several other writers whose figures are approximately the same. In our series only one definite instance among forty children was found. It is quite possible that some cases classified otherwise in in the absence of a suggestive history might actually belong in this category.

The following is a brief history of one case:

J. L., a white boy aged 8 years, entered Children's Hospital in March, 1939. He was known to have ingested on several occasions in the previous month a total of at least twenty "Guaiasin" tablets, which contain the guaiacol ester of phenyl-cinchonic acid, a chemical combination of cinchophen and

guaiacol. During the two weeks before admission he had been well except for gradually progressive jaundice. The day before admission he became acutely and severely ill with high fever and delirium. Examination on admission revealed a well-developed, fairly well-nourished child who was febrile and comatose. A generalized icterus was very noticeable. The liver and spleen were not palpable. Laboratory studies showed the urine to contain hyalin and granular casts with occasional white blood cells. The white blood count was 13,000. The icterus index was 170, the nonprotein nitrogen 25 mg. per cent, the serum calcium 12 mg. per cent, and the phosphorus 2.5 mg. per cent. The clinical diagnosis was acute yellow atrophy of the liver. The patient rapidly became worse, his fever climbed, the coma deepened, and purpuric areas appeared on the lower abdomen and hands. Edema of the eyelids, face, and legs and ascites were noted on the day of death, which was the fourth after admission. A small 460 gram liver was found at autopsy. It was grossly nodular and firm in areas, but in other areas it was necrotic. The microscopic examination (Fig. 10) showed extensive cirrhosis with widespread focal necrosis. There was severe destruction of liver architecture. Most of the scar appeared to be old but unevenly dispersed throughout it were zones showing various stages of necrosis and repair, some with increased vascularization or with hemorrhage.

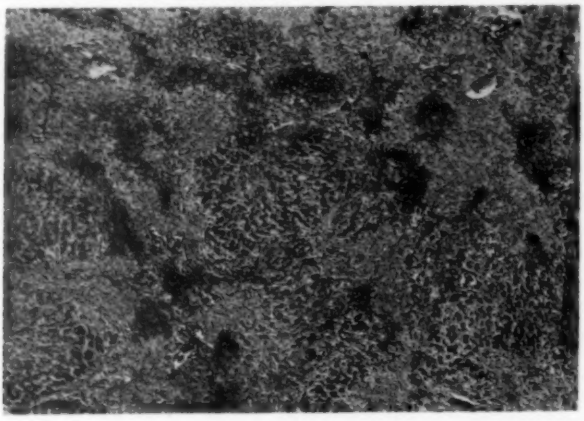

Fig. 10.—J. L. Cirrhosis due to cinchophen poisoning. The normal architecture is destroyed, so that more than one-half of the section shows scar tissue and focal areas of necrosis. Most of the scar appears to be old but dispersed unevenly throughout it are zones which show various stages of necrosis and repair, increased vascularity and hemorrhage. Liver cells are in isolated irregular nodules without a central vein. Section suggests repeated injury. (Masson stain, ×60.)

In the light of the history it would appear that this liver had been subjected to more than one period in which a hepatotoxic substance had destroyed areas of liver parenchyma, whereupon necrotic zones were replaced by cirrhotic scar tissue.

The pathologic picture does not differ significantly from what would be expected in an adult with toxic (postnecrotic) cirrhosis.

Fig. 10 is a photographic reproduction of a representative area of this liver.

HEPATOLENTICULAR DEGENERATION

An endeavor to survey comprehensively cirrhosis of all varieties will include mention of a small number of cases which have an equal or greater right to consideration among diseases of the central nervous system. These represent the condition to which Wilson[56] gave his name in 1912. What were probably the earliest two recorded cases were described by Gower in 1888 under the name of tetanoid chorea. Wilson[56] in 1912 attempted to absorb the "pseudosclerosis" of Alzheimer into his new syndrome. Two pathologic extremes exist between gross degeneration of the lenticular nuclei as described by Wilson and microscopic gliosis as described by Alzheimer. Hall[57] described a case with both, and gradations are now recognized under the term which he applied, hepatolenticular degeneration. A historical summary with references is given by Homburger and Kozol.[58]

The curious feature of the disease is the association of a degeneration in the brain, typically predominant in the lenticular nuclei but sometimes involving the cortex in lesser degree, with a marked but usually asymptomatic cirrhosis of the liver. The condition is rare. Strong[59] declares that a total of only fifty examples has been reported. Walsh[60] however, and Sweet, Gray, and Allen[61] suggest that it is not as unusual as has been supposed. Our finding of two proved and two possible cases in the files is in accord with this. Clinically[59, 62] the disease is characterized by insidious onset, usually in later childhood or young adult life. Although in its true form it is definitely heredofamilial in distribution, an essentially similar syndrome is encountered occasionally in acquired liver disease.[63-66] Bulbar palsy with dysarthria, hyperemotionalism, a progressive rigidity of the skeletal musculature, a coarse rhythmical tremor accentuated in emotional stress or in voluntary movements, and characteristic contractures of the hands, wrists, and feet are salient features. The mouth sags open with constant drooling and the facial expression is vacant or idiotic long before mental deterioration has reached a parallel degree. A zone of pigmentation at the limbus of the cornea, known as Kayser-Fleischer ring, is diagnostic when found. It is often missed without special examination. Loss of liver function may or may not be evident. Wilson stressed the silent nature of the inevitable cirrhosis but many authors[60, 61, 67-70] have since described cases in which evidence of liver disorder was present or even predominant.

CASE 1.—C. V. D., a white boy aged 12 years, was first seen in October, 1945. He had a family history that suggested that a sister had died at the age of 10 years from some sort of liver disease. Past history was negative. His present illness began two years prior to admission with bleeding tendencies. As time went on he developed stiffness of the joints and contractures of his hands. He was discovered to have a large spleen eight months before admission. A few weeks before entering the hospital he developed polydipsia and polyuria. Occipital headaches had been troublesome.

On examination the boy was listless, dull, and had great difficulty in enunciation. His sensorium was clear. He had numerous bruised areas. His

spleen was enlarged, firm, and not tender. The liver was enlarged. He had weakness in all extremities and his tendon reflexes were hyperactive. He had a urine of low specific gravity and a leucopenia. After discharge he developed progressive signs of basal ganglion disease and evidence of liver malfunction. A laparotomy was performed which disclosed a typical nodular cirrhosis of the liver. See Fig. 11 for the microscopic picture. The boy died a few hours after the laparotomy. A post-mortem examination was not granted.

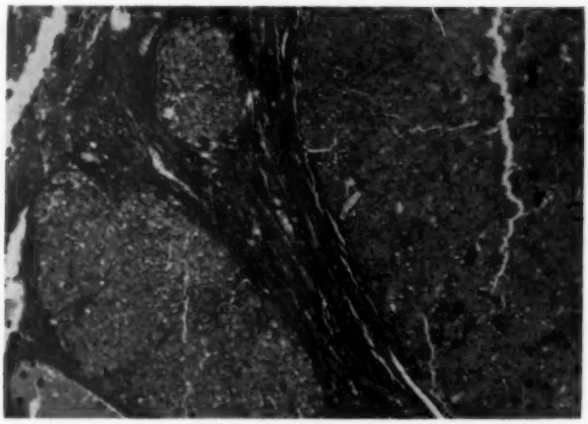

Fig. 11.—C. D. Biopsy, hepatolenticular degeneration. Liver cells, among which is a scattering of pycnotic nuclei, are divided into islands by large smooth bands of connective tissue. Note absence of central vein. Some liver cells show pressure necrosis. (Hematoxylin-eosin stain, ×60.)

Case 2.—C. G., a white boy aged 14, was first seen in October, 1934. His brother had died at the age of 6 years from cirrhosis of the liver in another hospital. He gave a history of the steady development of the classical picture of Wilson's disease for a period of seven years. The physical findings in the liver were those of advanced portal cirrhosis. There was extensive softening of both lenticular nuclei.

Discussions of the etiology of this condition usually have concluded that the disorder in the central nervous system is secondary to that in the liver. The nature of the cirrhosis is indistinguishable from that in ordinary portal cirrhosis. Although the lesions of the brain are most prominent in the lenticular nuclei, they are not always confined to that area. Rabiner and associates[70] suggest that the vascular endothelium constitutes a blood-brain barrier serving to protect the brain from noxious agents, that this barrier may be a part of the reticuloendothelial system generally, and that disease of the liver or spleen might serve to break down this barrier and leave the central nervous system abnormally vulnerable.

The diagnosis of hepatolenticular degeneration cannot be made definite, in most cases, without finding both the characteristic neurologic manifestations and some evidence of hepatic cirrhosis. The strong heredofamilial nature

of the disease, however, may support a presumptive diagnosis when such a diagnosis already has been made in some other member of the family. The diagnostic Kayser-Fleischer ring should be looked for. Liver function tests may sometimes prove helpful in establishing the presence of liver dysfunction. Liver biopsy may be resorted to in selected instances.

UNCLASSIFIED JUVENILE CIRRHOSIS

Seven cases encountered in this study are not classified for lack of clinical data.[6] Because they did conform to the usual anatomical types they could not be placed under an anatomical classification.

Two of them presented the clinical and biopsy findings compatible with a diagnosis of obstructive biliary cirrhosis due to congenital anomaly of the bile ducts. However, at laparotomy the major extrahepatic bile ducts appeared to be patent. It is quite possible the site of obstruction was intrahepatic or in extrahepatic ducts that could not be visualized during the operation. One child died at home and the other in the hospital. An autopsy was not obtained on either.

Two additional patients who died early in infancy and who developed jaundice soon after birth were found at autopsy to have diffuse fibrosis of the liver. Both were febrile during their period of hospitalization. Cultures of *Bacillus coli* were grown from the blood of each patient. One had nucleated erythrocytes in the peripheral blood and extramedullary hematopoiesis in the liver, but this may have been due to the fact that she was premature. No Rh data were obtained. The possibility that bacterial invasion of the blood stream was the cause of liver damage is good but not conclusive. Many pathologists agree that bacteremia will, in selected cases, result in cirrhosis of the liver (Moon,[71] Karsner,[1] and Moore[16]).

In the fifth of these unclassified cases the patient was found at autopsy to have diffuse, moderate fibrosis of the liver. The patient was born a month prematurely and lived only two months. Evidence of erythropoiesis was obtained from the peripheral blood and the autopsy specimens. She also had a positive blood culture for *Staphylococcus aureus* which was believed to be the result of an abscess on her back. The clinical findings were not sufficient to make a diagnosis of erythroblastosis and no Rh data was obtained in those days. Perhaps the bacteremia was the principal etiological factor.

The sixth patient is a boy who at the age of 5 months was discovered to have a prominent splenomegaly and lymphadenopathy. At an outside hospital he is known to have been given multiple blood transfusions and sent home. He suffered from several intercurrent infections, including otitis media and pneumonia, before coming to Children's Hospital. Here a biopsy of a large liver was obtained that showed quite extensive portal and diffuse fibrosis. Skin and lymph node biopsies did not help make a diagnosis. Clinical impressions of xanthomatosis and agnogenic myeloid metaplasia were never substantiated. The clinical and pathologic classification of this child remain undecided.

The seventh patient, a white boy, had a brother die at the age of 5 months with "liver trouble." He was hospitalized at the age of 9 months with a history of jaundice for two months. He was undernourished and underdeveloped. A splenomegaly and hepatomegaly were found. Laparotomy disclosed a smooth liver. On microscopic examination mild, diffuse fibrosis was found. The etiology is obscure. The anatomic findings are not like those in the usual anatomic classifications.

These cases serve to emphasize that good clinical and laboratory data are essential to accomplish an accurate classification. Knowledge of the pathogenesis and etiology of cirrhosis is not as yet sufficient to make classification of cases easy, even when data is available. It would be a mistake to think of "juvenile cirrhosis" only in its classic nodular form.

THE DIAGNOSIS OF JUVENILE CIRRHOSIS

Many papers have appeared which discuss the symptomatology and diagnosis of cirrhosis. Most of them emphasize adult findings. A brief review of the peculiarities of the condition in childhood and infancy is undertaken here.

Enlargement of the liver even in advanced cases has been an almost universal finding. This is in contrast to the findings in adults where a small liver is the usual finding in advanced cirrhosis. Obstructive biliary cirrhosis in children is nearly always due to congenital atresia of the bile passages, while in adults this is never true. Cirrhosis as a sequelae to fetal erythroblastosis seems well established from this study while a relationship of the two conditions for adults is not established although admittedly possible. The occurence of vascular spiders in the majority of adult patients has been emphasized by Bean[72] and by Patek, Post, and Victor.[73] In children with cirrhosis this physical finding is rare. A history of the ingestion of large quantities of alcohol for long periods of time is usual for people with adult nodular cirrhosis. Such a history is rarely encountered in children with the same variety of cirrhosis.

The importance of a careful clinical history cannot be overemphasized. The history of the ingestion of hepatotoxic agents that are powerful enough to cause cirrhosis is not likely to be elicited unless the interrogator has the possibility in mind. The cause of postnecrotic cirrhosis in the case reported in this paper was not suspected until autopsy. The patients with congestive cirrhosis with one exception (one with hepatic vein thrombosis) gave a history of prolonged and intermittent cardiac decompensation. The report of clay-colored stools since birth will always be available when the patient suffers from congenital atresia of the bile ducts, and it should be elicited. A history of syphilitic parents, of course, would cause immediate investigation of syphilis as the cause of symptoms in the newborn infant. To gain a knowledge of liver disease in other members of the family is imperative if such is the fact. It is important in evaluating suspected cases of cirrhosis to know about bleeding tendencies and of past episodes of jaundice. Data pertaining to the diet and development may be helpful in the study of, if not in the diagnosis of, juvenile cirrhosis.

Hepatomegaly, hepatomegaly with splenomegaly, jaundice, ascites, light-colored stools and dark urine are the common objective findings that draw attention to the liver as the site of disease. Prominent superficial abdominal veins, hemorrhoids, or other evidences of portal hypertension occasionally serve to focus attention on the liver.

Complete blood counts and routine urinalyses are essential in evaluating any case. The serology is essential to rule out syphilitic cirrhosis. Rh typing of the patient and parents should be accomplished to settle with a high degree of probability whether erythroblastosis is to be considered. Quantitative determination of Rh antibodies should be done if the clinical picture of erythroblastosis exists. In Negroes, careful and repeated search for the sickling tendency is indicated, because this form of anemia seems to be an occasional precursor of cirrhosis. Xanthomatosis usually shows characteristic changes in the skin or bones and if it or syphilis is suspected, skeletal films should be obtained. Liver function tests, if positive, will establish the presence of liver disease. They should always be obtained in suspected cases of cirrhosis not only as an aid in diagnosis but to help follow the progress of the disease. It is necessary to know when jaundice exists if it is obstructive, hematogenous, or hepatogenous. The required data to determine this, aside from the history, is history of bile in the stool, bile in the urine, or urobilinogen in the urine. The quantitative Van den Bergh also is helpful.

The diagnosis of obstructive biliary cirrhosis for all practical purposes in children depends on making a diagnosis of complete persistent obstructive jaundice. Once a diagnosis of congenital atresia of the bile ducts is established, one can conclude that obstructive biliary cirrhosis also exists. A history of jaundice from the time of birth or soon thereafter can be obtained. Clay- or white-colored stools from the time of birth is a universal finding. These babies are well nourished as a rule in spite of the jaundice. They often remain so for many weeks. Bleeding tendencies and evidences of portal obstruction develop late in the course of the child's short life. Jaundice and a high icterus index are prominent findings. Hepatomegaly, splenomegaly, and distention of the abdomen also are found. The laboratory findings substantiate the presence of an obstructive type of jaundice which in most cases is complete and persistent.

Nodular cirrhosis is usually an exclusion diagnosis. Most of the patients in this series had a clinical diagnosis of "Banti's disease," although some did not show the usual anemia or leucopenia. A history of bleeding tendencies, poor development, many infections, and an inadequate dietary intake may sometimes be obtained. Patek and Post[80] found the most common symptom to be insidious swelling of the abdomen. Two of the children whose cases are presented in this paper gave such a history. Jaundice often accompanies the terminal illness. The usual manifestations of Ganti's syndrome are present. Evidence of portal hypertension is usually prominent. In the final analysis a liver biopsy is required to make a certain diagnosis because the diagnosis depends on the anatomic findings. The findings are not constant enough to make a certain clinical diagnosis.

The diagnosis of congestive cirrhosis depends on the establishment of a diagnosis of cardiac decompensation which has been chronic and intermittent. The physical findings, in addition to those attributable to heart disease, are those which indicate the presence of portal hypertension. Sometimes the hepatomegaly, splenomegaly, and ascites are the result of both chronic passive congestion from cardiac decompensation and the portal obstruction of cirrhosis. An evaluation of the role played by each is difficult. In most cases the cirrhosis can only be suspected because it does not always result even though cardiac decompensation has been present for a long time.

Postnecrotic cirrhosis should not be diagnosed clinically unless the findings of cirrhosis are found and a definite hepatotoxic agent can be identified. Sometimes it can be differentiated from nodular cirrhosis by experienced histopathologists on the finding of liver nodules that are more irregular in size and less uniform in pattern from those seen in nodular cirrhosis.

The diagnosis of cirrhosis as a part of the disease of erythroblastosis fetalis may be suspected clinically if evidence of portal hypertension develops. It probably will be a pathologic diagnosis in most instances until more serologically proved cases are followed and reported.

The diagnosis of hepatolenticular degeneration depends on finding both the characteristic neurological manifestations of the disease and in addition some evidence of hepatic damage. The diagnostic Kayser-Fleischer ring should be kept in mind. In advanced cases the physical and anatomic findings are identical to those of nodular cirrhosis.

SUMMARY

Forty proved cases of cirrhosis from the records of The St. Louis Children's Hospital, have been classified and discussed. Clinical and pathologic findings have been outlined and brief comparison made with the picture in adults.

Cirrhosis in children is rare, but not so rare as has been supposed. Defined as a diffuse fibrosis of the liver, it can be brought about in a variety of ways, some of which depend upon inheritance and some upon major derangement in some other organ system. The classification used here is etiologic in general; its limitations are those of the material at hand, which, although unusually large, is not representative of all known forms of the disease.

Obstructive biliary cirrhosis is due almost always to congenital anatomic anomaly. Clinically it is distinguished by an obstructive type of jaundice in the newborn infant and pathologically by interlobular fibrosis, bile stasis, and moderate inflammatory infiltration.

Nodular cirrhosis usually develops in childhood rather than in infancy, and is insidious in onset. Jaundice and hepatosplenomegaly are the most constant findings. The atrophic stage is rare. The liver shows extensive perilobular fibrosis, focal regeneration, and mononuclear cell infiltration without bile stasis.

Cirrhosis is a rare sequela of erythroblastosis fetalis. In addition to the usual clinical and pathologic findings of erythroblastosis there is diffuse fibrosis of the liver.

Congestive cirrhosis is the result of repeated severe passive congestion of the liver that alternates with periods of relative compensation. Clinically it is overshadowed by the primary disease of the heart. The excess fibrous tissue is central to the lobule rather than diffuse or peripheral. Hyperemia and dilatation of the sinusoids are typical. The liver is enlarged rather than shrunken. Hepatic vein thrombosis as a cause of congestive cirrhosis is rare.

A variety of toxins are capable of causing necrosis in the liver, which, if it is not too extensive, is followed by fibrotic repair. There seems to be nothing distinctive about this sequence as it occurs in children.

Two typical cases of hepatolenticular degeneration are described. So far as the liver is concerned they are indistinguishable from ordinary nodular cirrhosis.

The incompleteness of our understanding of this field is emphasized by the presentation of seven unclassified cases which illustrate the difficulties in exact diagnosis.

We wish to express our thanks to the professor of pathology, Dr. Robert Moore, for making available to us all data and material on those patients who came to autopsy.

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THEPHORIN

Clinical Results in Allergic Children

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THE use of antihistaminic drugs in allergic diseases is based upon a theory which is yet to be conclusively proved. This theory postulates the liberation of histamine as a result of the union of the allergen and the sensitized cell in the shock organ. The resultant reaction supposedly produces histamine plus other physiochemical changes in the cell itself. Histamine liberation as a result of the allergic reaction cannot alone explain all the symptoms of allergy. Nevertheless, the recently introduced drugs which are able to neutralize the pharmacologic effects of histamine have proved themselves of great value in the relief of some allergic symptoms. The failure of these drugs to be universally effective only serves to emphasize again the inadequacy of the histamine theory as a complete explanation of the allergic reaction.

Benadryl and Pyribenzamine, the first antihistaminics produced in this country, have been followed by a plethora of many similar drugs evolved by pharmaceutical laboratories, each with claims of greater superiority and lesser percentage of side reactions. These compounds are phenolic ethers closely related structurally to Benadryl and Pyribenzamine.* From the reports of others and from our own unpublished observations it is evident that they produce similar but varying percentages of side reactions. The most important side reactions encountered are drowsiness and sleepiness, which seem to occur with Benadryl more frequently than with most of the other compounds. In our previous study of Benadryl[1] numerous other side reactions were listed, and occur with most of these drugs. Their depressing effect is not always disadvantageous when treating allergic diseases in children, in whom their sedative action is often desirable, particularly in asthma and eczema.

In an effort to overcome the drowsiness produced by these drugs, cerebral stimulants such as dextro-amphetamine, desoxyephedrine, and caffein have been used when indicated, especially in adults. A compound of Benadryl and Aminophyllin (Hydryllin-Searle) was found[2] to be superior to either Benadryl or Pyribenzamine from the standpoint of fewer and less severe side reactions. Aminophyllin exhibits an effective central nervous system stimulating effect in addition to its well-known ability to relax smooth muscle. This combination of

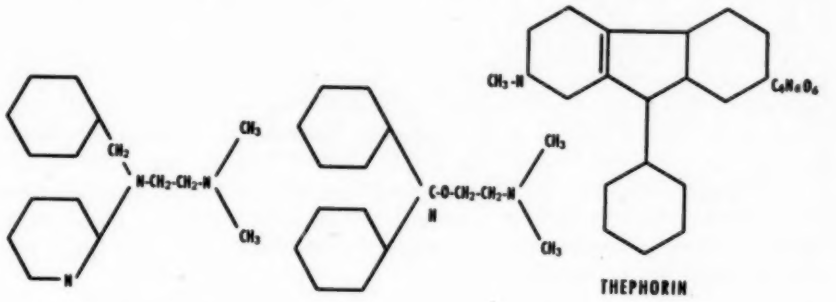
From the Allergy Clinic, Children's Hospital of Michigan.

*The following chemical compounds are similar in structure to Benadryl and Pyribenzamine, formulas of which are shown.

Antistine	Ciba
Decapryn	Merrill
Neo-Antergen	Merck
Neo-Hetramine	Wyeth
Histadyl	Lilly
Diatrin	Warner
Trimeton	Schering
Thenylene	Abbott

drugs produced a greater percentage of benefit not only in hay fever but also in noninfective asthma, in which patients the antihistaminics alone are far less effective.

Recently we have had the opportunity of studying an entirely new antihistaminic drug, characterized by a structure totally different from those previously reported, which, as pointed out, are all closely related. This drug is 2-methyl-9 phenyl-2,3,4,9-tetrahydro-l-pyridindine. The hydrogen tartrate salt is marketed under the name "Thephorin."* The structural formula of Thephorin is shown along with those of Benadryl and Pyribenzamine which are representatives of the older group of antihistaminics. Exhaustive in vitro and in vivo studies[3-5] have shown that this new drug is low in toxicity and high in antihistaminic effect. Pharmacologically the drug antagonizes the physiologic effect of histamine in experimental animals. It prevents histamine-induced contraction of the smooth muscles of the bronchi and intestines; it abolishes the effect of histamine on blood pressure and capillary permeability and is of value in preventing anaphylactic shock in the guinea pig. Acute toxicity studies in mice showed that it was about the same as Benadryl but only one-third to one-half as toxic as Pyribenzamine. There was no evidence of chronic toxicity.



Clinical studies with the drug by several previous observers[5-9] have been carried out almost exclusively on adult patients. These indicate a very high percentage of symptomatic relief, varying with different observers from 70 to 97 per cent in hay fever, 65 to 91 per cent in asthma and urticaria, and a significantly high percentage in allergic rhinitis and other allergic disorders. These observers reported that Thephorin produced fewer side reactions than other antihistaminics and caused drowsiness and sleepiness much less frequently than the older group of antihistaminics.

On the contrary, the majority of the side effects observed were due to its central nervous system stimulating effect, resembling similar effects produced by ephedrine and amphetamine. Our unpublished results[10] using Thephorin in 142 adults corroborates the observation of others that side reactions with this drug are slightly less frequent but much less severe than with other antihistaminics.

*Hoffman-LaRoche, Nutley, N. J.

In our series of adult patients, side reactions occurred in 30 per cent of the patients, but in only 8 per cent were they severe enough to warrant discontinuance of the drug. Clinical improvement occurred in 110 of 140 of our adult patients (77 per cent) treated for asthma, hay fever, allergic rhinitis, and urticaria.

The effect of the drug on allergic symptoms in children was presented in detail in one report.[6] Peters treated 142 patients, of which twelve were children 13 years of age or under. The results in all twelve children, some with hay fever others with asthma (pollen and nonpollen) were excellent. He reported no side reactions in this small group. Our preliminary study of this drug, begun in early 1948, was particularly stimulated by this remarkably favorable report of clinical relief with complete absence of side effects. A more extensive study of the drug in a larger group of children was therefore undertaken with great interest.

Dosage.—The drug is supplied in tablets of 25 mg. and in a syrup containing 10 mg. per teaspoon. Our case material consisted of patients seen both in the Allergy Clinic of the Children's Hospital of Michigan and in private practice. The dosage prescribed for younger children was one teaspoon of the syrup every three to twelve hours if necessary. Older children were given the tablets, 25 mg. every three to twelve hours as required, depending on symptoms.

Results of Treatment.—The effect of the drug was generally very definite. Relief was either marked and frequently complete or the drug was definitely ineffective. The mothers were usually quite certain as to the effect of the drug which, in the case of most of the children, was evaluated on objective symptoms. Relief, when produced, lasted from four to twelve hours. The effect of the drug was quite consistent in the same patient. This was in contradistinction to our previous experience with Benadryl, the effect of which was found to be variable in some patients at different times. In this series relief less than 50 per cent was noted as "no benefit."

TABLE I. THEPHORIN RESULTS IN ALLERGIC CHILDREN

DIAGNOSIS	PATIENTS	RELIEF OF SYMPTOMS				RELIEVED MORE THAN 50%	SIDE REACTIONS	
		100%	75%	50%	0 OR SLIGHT		PATIENTS	DISCONTINUED TREATMENT
Pollen H. F.	38	20	9	2	7	81%	10 = 26%	4 = 10%
Pollen asthma and pre-asthmatic cough	12	6	2	0	4	75%	1 = 9%	0
Perennial asthma noninfective	38	11	12	5	11	73%	8 = 20%	3 = 7%
Perennial allergic rhinitis	9	3	2	1	3	66%	2 = 22%	1 = 11%
Infantile eczema	4		3		1	75%		
Urticaria	8		4	3	1	87%		

Hay Fever.—Thirty-eight children having grass pollen or weed pollen hay fever were given the drug for symptomatic relief. Thirty-three (81 per cent) received 50 per cent or better relief. Many were receiving pollen desensitization and were given the drug for symptomatic relief on days when their symptoms were not under control. Others were new patients who received the drug in

an attempt to control symptoms while desensitization treatment was instituted. Even though some patients were thus receiving injection treatment, the action of the drug could be readily evaluated, since if relief occurred, it was usually prompt and definite within twenty to thirty minutes.

Pollen Asthma.—We treated twelve children with pollen asthma or preasthmatic cough. Eight (75 per cent) were relieved 50 per cent or more.

Perennial Asthma.—We treated thirty-eight children whose asthma was perennial in nature and noninfective in type. Twenty-eight (73 per cent) received very definite clinical benefit. These results are much better than with many of the other antihistaminics that we have used. Asthma complicated by respiratory infection responds poorly to Thephorin. We have made the same observation with many other antihistaminic drugs.

Perennial Allergic Rhinitis.—Nine children were treated with the drug, of whom six (66 per cent) were benefited 50 per cent or better.

Infantile Eczema.—Only four infants were avilable for trial with the drug. In three of these (75 per cent) there was definite relief of itching.

Urticaria.—In eight cases of urticaria in young children seven were very appreciably relieved by Thephorin. None of these were chronic cases, and it would be difficult to attribute the improvement in such cases to the drug alone. Acute cases of urticaria are well known to be of short duration. However, the drug was very definitely of benefit in reducing the itching.

We also used the drug in several children for the prevention of reactions following pollen injections. In four children in whom the drug was so used the tendency to such reactions was greatly reduced.

Side Effects.—Side reactions occurred as follows in our 109 patients:

Slight drowsiness	13
Severe drowsiness	2
Epigastric pain and/or nausea	4
Constipation	1
Restlessness and excitation	2
Total	22 patients

We were thus unable to confirm Peter's observation in regard to the complete absence of side reactions in children. In our 109 patiens there were 22 (21 per cent) side reactions. However, only nine (8 per cent) were severe enough to discontinue the drug.

In fifteen of the twenty-two children in whom side reactions occurred, drowsiness was the chief symptom. This in contrast to the observations of others and ourselves in regard to the side reactions to Thephorin in adults. In the older patients a sedative effect from Thephorin is seen much less frequently. The chief side reactions in adults consist of central nervous system stimulation and gastrointestinal symptoms.

It is apparent that Thephorin is an effective antihistaminic drug and a valuable addition to the measures available for the palliative treatment of allergic diseases in children.

Such new drugs in no way lessen the importance of adequate studies and subsequent specific treatment when indicated in these conditions.

SUMMARY

1. Thephorin, a new antihistaminic drug, differing structurally from previous evolved antihistaminics, has been evaluated clinically in 109 allergic children.

2. It was found to be very effective for symptomatic relief as follows:

Hay fever	81% relieved
Pollen asthma	75% relieved
Perennial asthma	73% relieved
Allergic rhinitis	66% relieved
Infantile eczema and urticaria	75% relieved

3. Thephorin produced side reactions in 20 per cent of this series. Reactions were seldom severe enough (8 per cent) to discontinue use of the drug. Thephorin has a mild sedative effect in children in contrast to the stimulating effect seen in adult patients.

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A CORRECTION

In the February issue of THE JOURNAL a case report was published entitled "Hycodan (Dihydrocodeinone) Poisoning" which title may have been misleading. It was not in any way the intention of the authors to create the impression that they have found Hycodan, in therapeutic doses, to be toxic. The authors wish to make clear that the article dealt with a single case of an unusually large overdose of Hycodan taken by an unguarded 3-year-old child—in fact forty times the recommended dose. The purpose of the article was to report the measures taken which brought about a complete recovery within a few days. The authors feel that perhaps a more responsive title for the article would have been: "An Accidental Case of Poisoning Following a Large Overdose of Hycodan—With Complete Recovery."

(Signed) Henry Rascoff, M.D.
March 31, 1949.

Case Reports

COOLEY'S ERYTHROBLASTIC ANEMIA IN A NEGRO GIRL

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NATCHEZ, MISS.

ERYTHROBLASTIC anemia as originally described by Cooley[1] is a progressive disease characterized by certain typical clinical features and changes in the hematologic picture and osseous system. Physical observations include pallor, underdevelopment, a large head with a Mongoloid face, flattened nasal bridge, prominent cheek bones, cardiac hypertrophy, hepatomegaly, and extreme splenomegaly.

The blood shows leucocytosis, severe hypochromic anemia, many erythroblasts, reticulocytosis, and decreased red cell fragility.

The distribution of bone changes in this clinical entity is generalized over the entire skeleton. The roentgenographic characteristics of the disease are widening and increased transparency of the long bones with thinning of cortices due to pressure from hyperplastic bone marrow. Medullary trabeculae are prominent. The skull shows thinning of the inner and outer tables. The outline of the outer table may be obliterated owing to atrophy from pressure by thickened diploe. The cancellous diploic bone is thickened, and closely packed striations resembling fine bony spicules situated perpendicular to the outer table in radial patterns are seen. The skull vault is thickened due to hyperplastic, hematopoetic components of the diploe.[2-5]

Cooley[6] and others who have investigated this anemia have not held the opinion that it is race-limited, although the disease is familial. Studies of Italian families by Dameshek[7] have revealed cases ranging in severity from Cooley's erythroblastic anemia to cases with mild hypochromic anemia, target-oval and stippled cells, and decreased red cell fragility. These syndromes, inherited as a simple mendelian dominant, showed a high incidence of transmission in the offspring. Valentine and Neel[8] conducted a genetic study which favored the hypothesis that the mild state is due to heterozygosity for a factor which, when homozygous, results in a full-blown erythroblastic anemia.

There have been several authentic cases of erythroblastic anemia reported in races other than the Mediterranean group. These include a case in an English child,[9] three cases in Chinese,[10, 11] and one in an Indian boy.[12] Dameshek[7] mentions one case occurring in a Negro boy seen at the Mt. Sinai Hospital in New York. Two other cases in Negroes have been reported, one by Stiles,[13] another by Faber.[14]

The prognosis of Cooley's anemia is unfavorable and treatment is unsatisfactory. One has to rely on blood transfusions to keep the hemoglobin above the critical level of 5 Gm. per cent. Good effect from splenectomy on identical Greek twins was observed by Govan.[15] Following the procedure, they required only one-third to one-fifth as much blood to maintain their hemoglobin above a critical level, and their general condition improved. However, the apparent results from these cases would not seem to justify it as a routine procedure. Blackfan and Diamond[16] state that splenectomy is contraindicated as it has not been followed by retardation in the progress of the disease, and suggest that the anemia may progress more rapidly.

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Fig. 1.

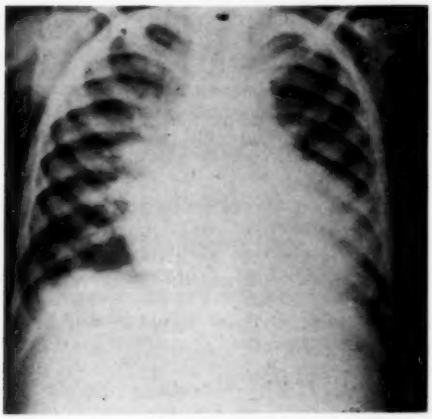

Fig. 2.

Fig. 1.—Front view of patient, showing palpable extent of spleen and liver.

Fig. 2.—Erect posterior-anterior view of the chest. Moderate enlargement of the heart, generalized in all diameters, is seen, with lung fields showing no definite evidence of pulmonary edema. Ribs and shoulder girdle show increased extent and prominence of trabeculation of marrow cavities, and thinning of cortex.

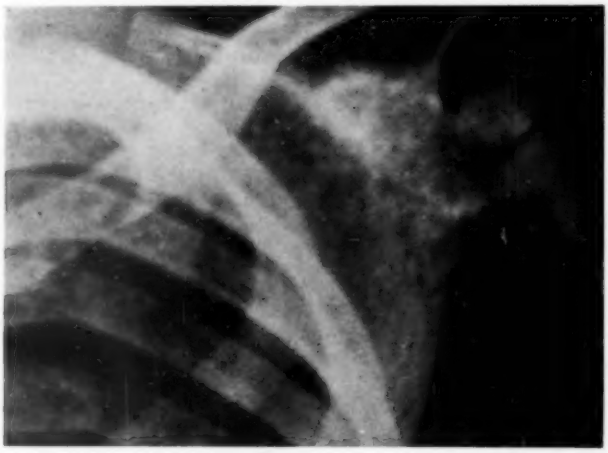

Fig. 3.—Inset of Fig. 2, showing bone changes in greater detail.

REPORT OF CASE

M. L. R., a 6-year-old Negro girl, was referred to the hospital on April 19, 1948, by Dr. W. B. Worley. She had had a cold with cough and chest pain for a month. The mother stated that she had a poor appetite and had been thin all her life. She had been in this hospital on Sept. 25, 1945, for a fractured humerus, and again in March, 1947, for bronchopneumonia. At that time she was found to have a severe anemia, but studies were inadequate to classify it. However, numerous nucleated red cells were observed in blood smears and she was given 750 c.c. of blood in three divided doses. The mother, father, and four siblings were living and well.

Physical examination on April 19, 1948, revealed an undernourished, pale, Negro girl not acutely ill. Her head was large, especially in the parietal regions, and she had a Mongoloid face (See Fig. 1). Blood pressure was 104/80. There was a systolic murmur over the entire precordium and the heart was enlarged to the left. The liver and spleen were both enlarged, being palpable 5 cm. below the costal margins. There were no other significant physical findings.

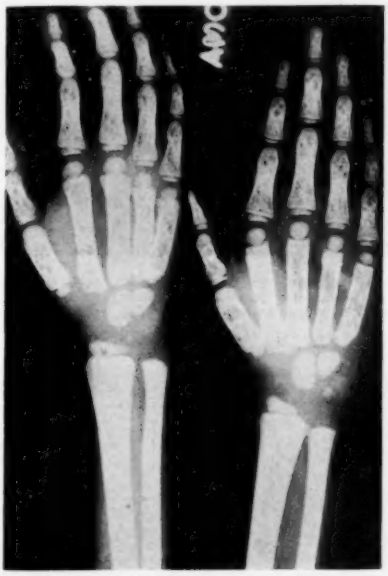

Fig. 4.—Views of both hands and wrists. The marked increase in extent and prominence of trabeculations in medullary portions of bones, is seen, with marked, uniform thinning of cortex surfaces. Only three carpal bones are ossified, suggestive of retarded maturity for chronological age.

The blood count showed 1.8 Gm. hemoglobin, 850,000 red cells, 15,650 leucocytes with 64 segmented neutrophiles, 19 stabs, 1 juvenile, 15 lymphocytes, and 1 monocyte. There were 507 nucleated red cells per 100 white cells. The red cells showed marked poikilocytosis, anisocytosis, hypochromia, and polychromatophilia, with many target cells (See Fig. 6) and many Howell-Jolly bodies, stippled red cells, and Cabot's rings. The sickling test was negative on four occasions. Platelet count was 250,000, reticulocyte count 5.4 per cent. The erythrocytic fragility test was reported as follows: hemolysis on patient begins at 0.34 and is not complete at 0.28. Hemolysis on control begins at 0.42 and is complete at 0.30. Icteric index was 14.4.

Smears of sternal marrow showed marked hyperplasia of erythroid elements, the myeloid/erythroid ratio being 1/20.

Results of x-ray films made on this patient were reported as follows:

"Skull: There was marked thickening of the diploe throughout the entire extent of the calvarium, with striations situated in a radial pattern.

"The hands showed swollen appearance of tubular bones, with cortices thinned and increased prominence of trabeculae of the medullary cavities. Only three carpal bones were present, suggestive that bone maturity may be slightly

Fig. 5.—Skull, showing thinning of the tables, with marked hyperplasia and thickening of the diploe. The radiate striations perpendicular to the diploe are suggestive of advanced hyperplasia of hematopoietic elements.

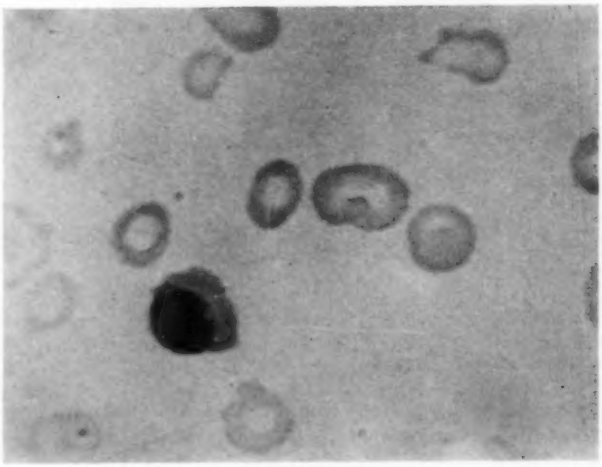

Fig. 6.—Smear of peripheral blood showing erythroblasts, hypochromic, macrocytic erythrocytes, and target cells.

retarded. The chest showed moderate, generalized enlargement of the heart in all diameters. Lung fields appeared clear. In all the bones of the thoracic cage and shoulder girdle, were seen marked thinning of bone cortices and increase in prominence of the trabeculae of the medullary cavities.

"Similar changes were seen in spine, pelvis, and lower extremities.

"Impressions: Advanced hemolytic anemia, type undetermined, the type of which requires the following differential diagnosis; (1) Cooley's Mediterranean anemia; (2) sickle cell anemia; and (3) familial hemolytic (spherocytic) anemia."

Treatment of this patient has consisted simply of repeated transfusions in approximately 200 c.c. doses. After receiving 1,000 c.c. of whole blood over a six-week period, her hemoglobin was 8.5 Gm., red blood cells 2,930,000.

She showed considerable improvement on this treatment and was discharged to return at monthly intervals for examination and transfusions.

SUMMARY

1. A review of the literature on Cooley's erythroblastic anemia is given.

2. A case occurring in a Negro child is reported to illustrate further that the disease is not limited to individuals of Mediterranean origin.

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CONGENITAL CYSTIC DISEASE OF LUNG IN INFANCY

Report of a Case With Necropsy Findings

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CONGENITAL cystic disease of the lung is not common at any age and rarely is diagnosed in infancy unless the condition has given rise to symptoms. The condition in recent years often has been treated surgically. The case to be presented is of a male baby who showed, shortly after birth, a sternal retraction which progressed in a few weeks to the development of a funnel type of chest. This chest deformity was brought about by a polycystic condition of the upper lobe of the left lung. The death of the child occurred at 6 weeks of age and the clinical history and autopsy findings are presented herein.

The earliest report of cystic disease of the lung was by Bartholinus[1] in 1687. The first real contribution to the literature of this pulmonary condition was in 1925 when Koontz[2] collected 108 cases from the literature, 26 of which occurred in the first ten years of life, and of these, sixteen were in the first year. Later, many papers appeared describing individual cases. By 1937, Wood and associates[3-7] had added forty-eight surgically treated cases. In the same year, Schenck[8, 9] collected a total of 381 cases from the literature. Up to the present time, additional single case reports have brought the total to about 450.

REPORT OF A CASE

L. D. M., a 6-week-old male infant with a history of dyspnea, cyanosis, and difficult passage of stools of five weeks' duration, was admitted to the Children's Hospital of Pittsburgh on May 4, 1948, to the service of Dr. E. R. McCluskey. There were no episodes of upper respiratory infection. On admission the infant appeared malnourished, underdeveloped, and in moderate respiratory distress with cyanosis except when at rest. The temperature was 98.6° F., pulse 126, and respirations 26.

The thorax had a funnel type deformity and a large left hemithorax. Infrasternal, intercostal, and a slight suprasternal retraction were marked on inspiration. The trachea was shifted well to the right. The mediastinum was also displaced to the right and the apex beat of the heart could be palpated at the left sternal border. Resonance over the left chest was almost tympanitic, while the right chest was hyporesonant except for a dullness over the site of the heart. Breath sounds were distant over the left chest, absent over most of the anterior right chest, and bronchial over the left lateral and posterior chest areas. The abdominal wall was flabby and possessed little muscular tone. Bilateral indirect inguinal hernias were present. The remainder of the physical examination was essentially negative.

The laboratory results showed an essentially normal urine. Blood examination showed a hemoglobin of 9.4 Gm., red blood cell count of 3,200,000, and a white blood cell count of 13,600 with 56 per cent granulocytes and 44 per cent lymphocytes.

Roentgenogram examination of chest showed normal bone-contours except for a marked indentation at the base of the sternum (Fig. 1). The heart, mediastinal structures, and trachea were displaced into the right lung field, with

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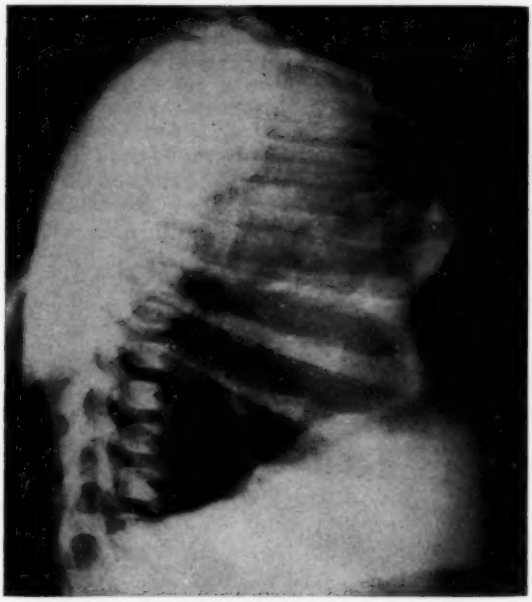

Fig. 1.—Roentgenogram showing deformity of sternum and emphysema of the left upper lobe of lung.

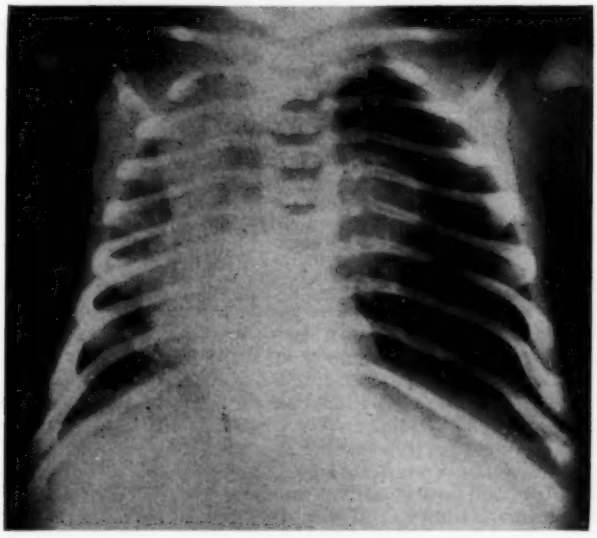

Fig. 2.—Roentgenogram showing cyst in left hilar region and emphysema of left lung field with displacement of heart and mediastinum to the right.

the right border of the heart almost approximating the right lateral chest wall. In the left hilar region there was a round opacity suggestive of a cystic structure which measured 2.5 cm. in diameter (Fig. 2). The left lung field was emphysematous with the exception of a small area of increased density immediately caudad to the area of left hilar opacity. The impression was that of a left hilar cyst with emphysema of the upper and lower lobes of the left lung.

Bronchoscopic examination demonstrated a trachea deviated to the right, clear right and left main stem bronchi, and a smaller than normal left main bronchial orifice which did not permit passing of the bronchoscope.

The course of the patient was downhill with progressively increasing air hunger, dyspnea, cyanosis and rapid pulse. Temperature elevation was never over 100° F. The respirations ceased on the seventh hospital day.

Fig. 3.—Gross specimen revealing an emphysematous left upper lobe with an attached accessory lobe and a compressed left lower lobe. The right lung shows marked compression with peripheral emphysema.

The necropsy was performed two hours after death. The body was that of an emaciated, poorly developed, white male child measuring 55 cm. in length. Bilateral indirect inguinal hernias were present. There was an enlarged left hemithorax. Examination of the neck and upper thorax revealed the trachea deviated to the right. The lower end of the sternum showed a concavity involving its inner surface. The abdominal muscles were of poor tone. The mediastinum together with the left lung were markedly shifted to the right and the right lung was compressed to a smaller size than normal. The left lung, measuring 11 by 8 by 5 cm., showed an anomalous lobation. It consisted of the two main lobes, upper and lower, and a small accessory lobe partially separated from the upper lobe (Fig. 3). The upper lobe filled a large part of the left thorax and its median border was located 3 cm. to the right of the midline. On sectioning, the cut surface of the upper two-thirds of this lobe showed numerous cysts of varying size. The cysts varied from 2 mm. to 25 mm. in diameter

(Fig. 4). The largest of these cysts, measuring 2.5 by 2 cm., extended outward from the hilus and occupied one-third of the inner part of the lobe (Fig. 4). This cyst lay directly over the main bronchus supplying the upper lobe. The cavity contained yellowish gelatinous mucus and had a thickened, corrugated surface which in two or three places communicated with adjacent underlying bronchi. The lower one-third of the cut surface of this lobe appeared emphysematous. The bronchus supplying the left upper lobe was patent and measured about 4 mm. at its origin and about 2 mm. at the middle of the lobe. The lower lobe, measuring 5 by 3 by 3 cm., was small and was displaced by the excessively expanded upper lobe into a position posterior to and left of the heart. It had a dark reddish color, was firm, and possessed little air-holding tissue. This lobe on section appeared firm but not consolidated and was supplied by a bronchus which measured 3 mm. in diameter at its origin on the medial surface. The accessory lobe (Fig. 3), measuring 4.5 by 3.5 by 1 cm., was attached for 1.5 cm.

Fig 4.—Section of cut surface of left upper lobe showing hilar cyst with cystic dilatation and emphysema of surrounding pulmonary tissue.

at the hilar surface to the left upper lobe. Its free border was divided into three irregular scallops. It was dark reddish blue in color and firm. On section, the tissue appeared solid and not air-holding. This lobe was supplied by a branch of the bronchus to the upper lobe which was about 2 mm. in diameter at its origin.

The right lung measured 9.5 by 6 by 4 cm. and showed a normal lobation except for an incomplete separation of the middle from the upper right lobe. With the exception of an emphysematous, pinkish-white area at the periphery of the lateral surface of the middle lobe, this lung showed moderate expansion

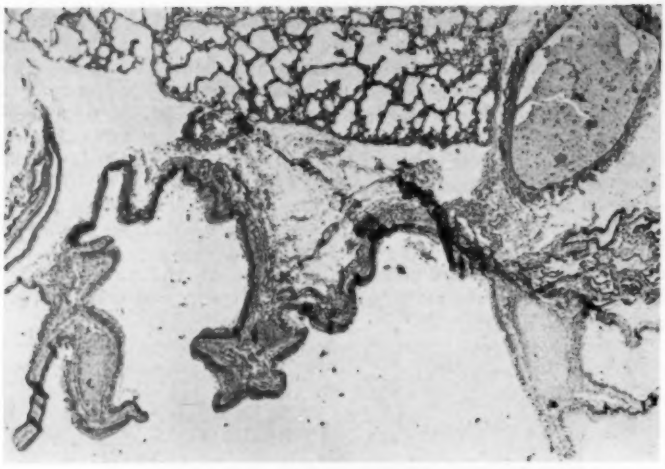

Fig. 5.—Cross section of upper lobe of left lung showing papillary projection of cyst wall. (Hematoxylin and eosin stain, ×30.)

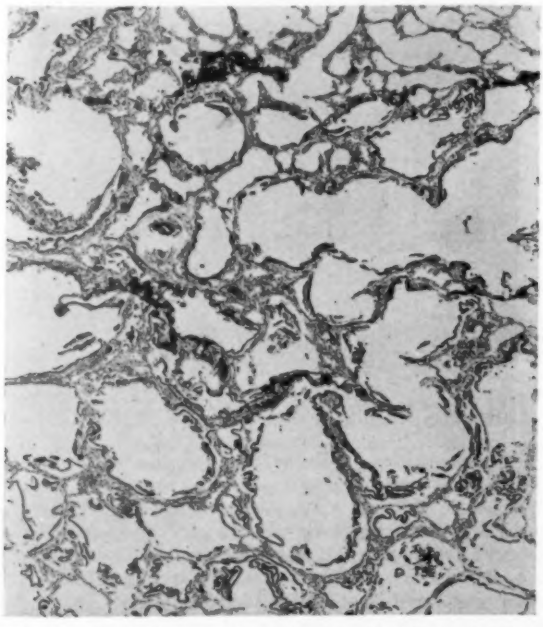

Fig. 6.—Cross section of upper lobe of left lung showing dilated terminal bronchioles, respiratory bronchioles, and acini. (Hematoxylin and eosin stain, ×30.)

and appeared firm and reddish in color. On section the organ appeared somewhat more solid than normal, but fairly air-holding. The other findings were essentially normal.

Anatomic Diagnoses.—Diagnosis was cystic disease of upper left lobe of lung; funnel-shaped deformity of chest; shifting of mediastinum to right; acute dilatation of right heart; emphysema; partial atelectasis of the lower lobe of left lung and of the right lung; bilateral inguinal hernias.

Sections were examined from all parts of both lungs. Microscopically, these fell into two groups: (1) polycystic in type, and (2) possessing architecture of normal lung with superimposed lesions of primary atypical pneumonia of unknown etiology.

In Group 1 the pleura was normal. The cystic dilatation was primarily in the bronchial tree and pronounced in the terminal bronchi and respiratory bronchioles (Fig. 5). The bronchi had a somewhat hypertrophied epithelium which stained deeply and in some areas was desquamated. A few of the larger bronchi contained a pink staining mucus. The alveoli which remained intact were relatively few in number and markedly dilated. The lining of the large cyst consisted of villuslike projections of bronchial wall with a thick connective tissue core covered with high columnar epithelium having prominent cilia. In the depressions between the bases of the papillary outpouchings, adherent pink mucoid masses were observed. The adjacent lung tissue showed dilated respiratory bronchioles and a few dilated alveoli. It was difficult to differentiate respiratory bronchioles, small terminal bronchioles, and alveoli because the majority of the dilated spaces were ballooned to many times their normal size (Fig. 6). The remainder of the lung showed a normal architecture upon which was superimposed a primary atypical pneumonia; the alveolar walls were thickened by an infiltration of round cells which had materially reduced the alveolar spaces. In some areas a compression atelectasis was present. The alveoli contained desquamated, hypertrophied, lining epithelial cells and erythrocytes. The other organs appeared essentially normal.

DISCUSSION

In our patient the abnormalities of chest referable to alterations in pulmonary structure were present at birth; consequently, the condition may be classed as congenital cystic disease regardless of the mode of pathogenesis. Various theories which have been enumerated by Müller[10] and by King and Harris[11] have been suggested for the origin of congenital cystic disease of the lung. One of the theories which has been widely accepted is a lack of canalization in small areas of the solid, cellular bronchioles present in the early developing lung. It is probable, however, that such factors as infection, anomalous lobation, and blood supply also play a considerable role in the formation of pulmonary cysts. When a bronchiole becomes occluded, expansion may occur above and below the block either because of increased air pressure or accumulation of mucoid secretion, so that primary cyst formation is usually associated with emphysema of the contiguous lung. This latter condition was brought about in our case by pressure of the large cyst on the main bronchus of the upper left lobe. The communications which existed between the large cyst and other adjacent bronchioles did not materially relieve the intracystic pressure because of the retained mucus.

All cysts of appreciable size are lined with papillary projections of bronchial epithelium, which feature was prominent in our case. It is readily understandable how symptoms of dyspnea can occur by obstruction in the lung. In those patients in which pressure is exerted on the heart, cyanosis may also be a symptom.

The differential diagnosis may implicate almost any pulmonary disease, e.g., acute infections, neoplasm, localized empyema, tuberculosis, hydatid cysts, and diaphragmatic hernias. The diagnosis in our patient was fairly obvious from x-ray films, but the sudden death of the child, probably from the associated viral pneumonia, occurred before surgical intervention could be consummated.

SUMMARY

Cystic disease of left lung, in an infant dying at 6 weeks of age, resulted in deformity of the sternum and displacement of the mediastinum, heart and left lung to the right. Necropsy revealed an associated primary atypical pneumonia of undetermined origin.

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TETANUS OF THE NEWBORN INFANT

Report of a Case With Recovery

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Cedar Rapids, Iowa

TETANUS neonatorum, which carries a very high mortality rate, has fortunately become a rather rare disease in this country. Cases of recovery, therefore, seem worthy of reporting.

CASE REPORT

On Aug. 30, 1948, a normal female baby was delivered spontaneously at a farmhouse. The birth weight was 6 pounds. The umbilical cord was tied by the attending physician with the usual umbilical tape (cloth). The navel was kept covered with a navel band. The cord came off on the fifth day and the stump looked clean; on the ninth day it appeared well healed. On the tenth day the baby became irritable but took the bottle well. The same evening she vomited once. On the eleventh day the parents noted that the baby held her fists tightly clenched and seemed to "make grimaces." They also thought the baby was unusually "strong," misinterpreting beginning rigidity as muscular strength. By the thirteenth day the baby was very fussy and had "spells" of clenching her fists. A drop of blood was noted on the navel. Profuse perspiration of the forehead and spells of "straightening out" frightened the parents. The temperature was 100° F. rectally. The baby continued to take the bottle fairly well but vomited on occasions. In the afternoon of that day, the mother heard the baby "panting terribly fast." She found the baby covered with perspiration and rather "stiff." The temperature was 106.2° F. rectally. The baby was taken to the hospital; during the trip she suffered three spells of "doubling up."

Course in Hospital.—On admission, the outstanding symptom was a marked, generalized rigidity. The following findings, present only in part when the baby was first seen, became more pronounced and typical of tetanus on the second and third day of hospitalization: The forehead was wrinkled, there was a risus sardonicus, the neck muscles were taught, and there was opisthotonus. The abdominal wall was boardlike; the extremities were hyperextended. The fists were tightly clenched and the toes spread out in fanlike fashion. The baby could be lifted up from the crib like a "wooden doll." She weighed 5 pounds, 4 ounces.

Three diagnostic possibilities were considered: tetany of the newborn, intracranial hemorrhage, and last, because of its rarity, tetanus neonatorum. Blood was drawn from the femoral vein for a calcium determination and 10 c.c. of calcium gluconate were injected. This did not produce any relaxation. The calcium value was 11 mg. per 100 c.c. A lumbar puncture was unsuccessfully attempted. Repeated the next morning, it yielded xanthochromic fluid under normal pressure, containing 1,200 red blood cells per cubic millimeter and no leucocytes. In retrospect, it was, of course, realized that the blood in the spinal fluid was traumatic. Bilateral subdural taps failed to reveal any bloody fluid. By now, symptoms typical of tetanus had become so pronounced that there was no more doubt about the diagnosis. 10,000 units of tetanus antitoxin were injected intramuscularly; this was repeated the following day. Chloral hydrate,

From the Department of Pediatrics, St. Luke's Hospital.

5 gr., was administered in oil per rectum every four hours; 1 c.c. of magnesium sulfate in 50 per cent solution was injected intramuscularly every six hours. Sodium phenobarbitol, in doses of ⅛ to ¼ gr., was given hypodermically as necessary to supplement the effect of those drugs. Penicillin, 10,000 units, was given intramuscularly every three hours.

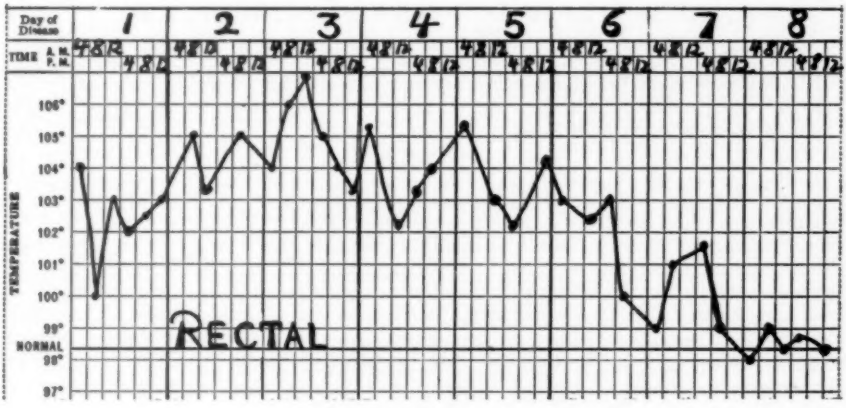

Chart I.

For the next twenty days the clinical picture was dominated by nearly constant rigidity which did not even leave the baby entirely when she slept. The slightest disturbance would produce "tremors" and increase in tonicity. The temperature is recorded in Chart I. Feeding at first was by nasal gavage but much of the formula (even when thickened with Pablum) was regurgitated. On the sixth hospital day the baby nursed fairly well from the bottle, but regurgitation persisted. By the tenth day, she took 2 ounces of a skimmed milk formula with Dryco and dextrose. The fluid intake was supplemented by subcutaneous injections of 5 per cent glucose in water and normal saline. On the eleventh day stools containing mucus were noted. It was believed that this may have been due to the continuous rectal administration of chloral hydrate. The drug was stopped and replaced by phenobarbitol sodium. Feedings were replaced by boiled water only. Whole blood, Amigen, and electrolytes were given intramedullary into the tibiae. On the fourteenth day the injections of magnesium sulfate were discontinued, after a slough had developed on one of the buttocks. By the fifteenth day severe diarrhea was present. The baby became considerably dehydrated. Blood, plasma (from the hospital's blood bank) and electrolytes were given intravenously, intramedullary, and (twice) intraperitoneally (glucose and saline only). The diarrhea lasted about ten days, then subsided. In the meantime, the baby's rigidity had greatly improved. By the sixth week recovery was steadily progressing; the baby was relaxed and gaining well. However, she continued to keep her fists clenched, possibly by now due to habit. She was discharged from the hospital on the sixtieth day, weighing 6 pounds, 11 ounces.

Laboratory studies showed a white blood count on admission of 14,500 cells per cubic millimeter with normal differential count. The hemoglobin was 11.5 Gm., the red blood count 3,030,000 cells per cubic millimeter. During the height of the diarrhea, the hemoglobin fell to 7 Gm., the red blood count to 2,650,000 cells per cubic millimeter, the white blood count was 12,900 cells per cubic milli-

meter. On discharge, the hemoglobin was 13 Gm., the red blood count 4,700,000 cells per cubic millimeter, and the white blood count 8,300 cells per cubic millimeter.

The patient returned a week later with a temperature of 105° F., severe clonic convulsions, and evidence of respiratory infection. Recovery was uneventful. The baby has been well ever since. At present (December, 1948) she weighs 10 pounds, 14 ounces. Physical examination showed her to be in perfect health.

COMMENT

There are many single reports of tetanus neoatorum in the literature, most of them with fatal outcome. There are only a few reports of larger series (Hines,[1] Jenkins,[2] Bratusch-Marrain,[3] and Jones[4]). The chief problem in this disease remains effective treatment. Perusal of the literature reveals that there really is only one drug which has lowered the mortality rate substantially, namely, magnesium sulfate. The use of this chemical in the treatment of tetanus of the newborn infant was first advocated by Bratusch-Marrain[3] in 1923. Between the years of 1906 and 1921, prior to its use, this author reports the loss of twenty-seven out of twenty-eight babies. From 1922 to 1923, he enlarged his series of patients by ten additional cases,[5] four of which survived. In the American literature, Hines[1] and Muelchi,[6] both in 1926, corroborated the effectiveness of the drug. In 1928, Smith[7] reported a case with recovery and was quite impressed by the effect of magnesium sulfate on the tetanic spasms. The actual value of antiserum, unless given very early after invasion of the organism, must still be considered doubtful. It should, of course, be administered in any case.

If called on to advocate a "standard" treatment, we would suggest the following routine:

1. Antiserum, 30,000 units, intramuscularly, to be repeated once or twice.
2. Adequate sedation with chloral hydrate, 5 or 6 gr., given every four to six hours as oil retention enema, with or without equal amounts of sodium bromide.
3. Magnesium sulfate, 50 per cent solution, 1 c.c. every six hours, given deep into the muscle.
4. Sodium phenobarbital, hypodermically, in addition to above, as needed to secure sedation.
5. Penicillin in oil every twenty-four hours.

SUMMARY

A case of tetanus neonatorum with recovery is reported. The use of magnesium sulfate is advocated. A "routine" treatment is suggested.

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Clinical Conference

CLINICAL CONFERENCE OF THE DEPARTMENT OF PAEDIATRICS, VANCOUVER GENERAL HOSPITAL

Case 1. A Case of Hemolytic Anemia in a Premature Infant

DR. PETER RANSFORD (Resident in Paediatrics) for DR. REGINALD WILSON (Associate in Paediatrics).—This white male infant was born two months premature on July 2, 1947. He was the first child and weighed 3 pounds, 4 ounces at birth. Mother, father, and child were Rh positive. The genotypes are detailed in Fig. 1. No atypical agglutinins were demonstrated. There is no history of jaundice or anemia on either side of the family. Except for a slight degree of physiologic icterus, the child was at no time jaundiced and did not bleed. However, he gradually became more pale until on Aug. 17, 1947, the hemoglobin was 54 per cent (7.04 Gm.). There was no splenic or hepatic enlargement noted at this time. He took his nourishment well and his diet was supplemented with multivitamin emulsion and iron. The stools and urines were normal. Two transfusions were given over a period of two weeks (August 18 to September 3) and after sixty-five days in the hospital he was discharged with a hemoglobin of 67 per cent.

He stayed at home for three weeks and during that time the pallor returned and on September 25 he was readmitted to the hospital with a hemoglobin of 55 per cent. Examination then revealed a pale infant weighing 7 pounds, 1 ounce. The abdomen was somewhat protuberant and the spleen was palpable. The remainder of the examination was negative. He was again transfused, which raised his hemoglobin to 60 per cent.

On September 30 refined liver extract was commenced and with this, plus oral iron, the hemoglobin hovered around 55 per cent but gradually fell during the next month to 45 per cent.

On October 27, the spleen was recorded as moderately enlarged with no other remarkable findings save pallor. He had continued to gain weight and now weighed 8 pounds. On November 3, in addition to liver and iron, folic acid was commenced with a subsequent rise in reticulocytes (see Fig. 1), and hemoglobin reached a maximum of 91 per cent by November 20 (an increase of from 50 per cent to 91 per cent in sixteen days). On December 2 the child was discharged on folic acid alone. The appetite was good and the color markedly improved. The spleen was still enlarged 3 fingerbreadths below the costal margin. Weight on discharge was 10 pounds.

Additional laboratory investigation revealed: red blood cell fragility normal on child and both parents, with no evidence of spherocytosis; volume index of .91; saturation index of .98; hematocrit 23 per cent. White blood count and differential were always within normal limits; icterus index on

November 5 was 18; Kahn, negative; sedimentation rate on October 28 was 5/16 (Westergren); stomach juice, histamine-fast achlorhydria; stools, normal in color; the urines were repeatedly negative for bile and showed urobilinogen values up to 1/64 dilution.

Bone marrow on November 1 gave a megaloblastic reaction (Figs. 2 and 3) and on November 18 was normal.

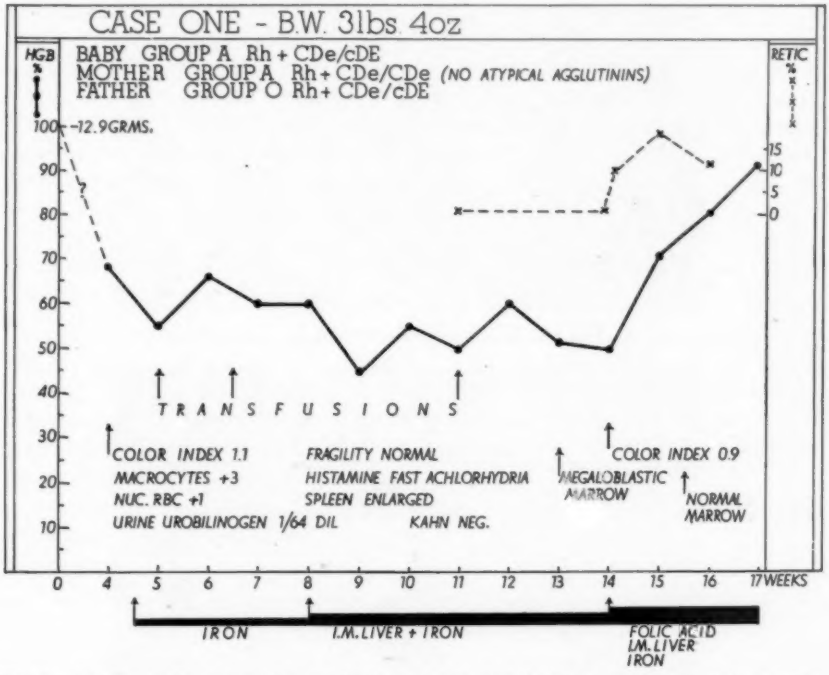

Fig. 1.—Diagrammatic representation of the main clinical features, treatment, and progress.

DISCUSSION

Dr. A. W. Bagnall (Associate, Department, of Medicine).—This is the case of a premature infant who developed a severe anemia. The onset of the anemia was earlier than the usual anemia of prematurity. It was a macrocytic anemia and was associated with splenomegaly. Nucleated red cells were present and there was an increased urobilinogen excretion in the urine. It was a hemolytic type of anemia. There is no evidence that this was due to Rh incompatibility, yet one cannot say that some as yet unidentified agglutinin was not present. At any rate, the process was quite severe and prolonged as, in spite of transfusions, iron and refined liver extract, the infant remained anemic (hemoglobin 50) four months after birth.

There was a reticulocyte response from 2½ to 11 per cent after one day's treatment with folic acid. It seems unlikely that this was wholly due to this

treatment, but it would appear from the reversion of the bone marrow to normal after folic acid therapy and the quick and sustained rise in hemoglobin which occurred at this time, that there was a deficiency of that factor.

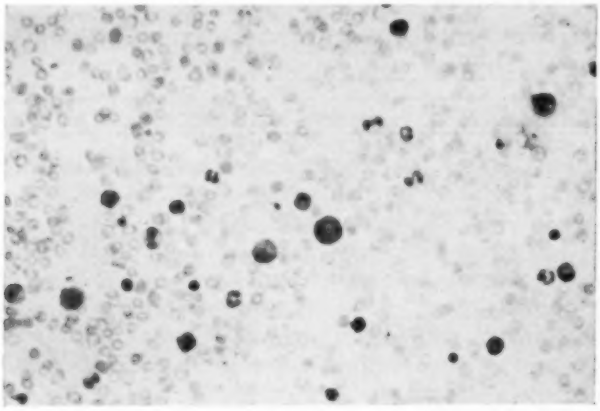

Fig. 2.—Low power magnification of the bone marrow smear.

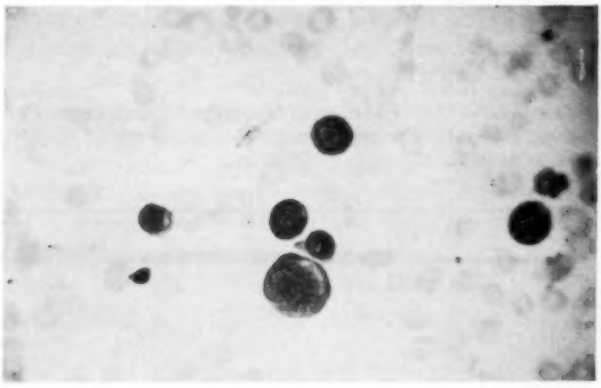

Fig. 3.—High power magnification showing typical "megaloblast."

In summary one must conclude that this child suffered a hemolytic (macrocytic) type of anemia due to some unidentified hemolysin. Certainly there is no positive evidence that this was due to excessive fragility or Rh compatibility. It would seem also that there was defective blood regeneration and that this was not improved by liver extract or iron but that regeneration *did* take place coincidentally with the administration of folic acid. We must conclude, therefore, that we are dealing with a hemolytic anemia in a premature infant with the secondary development of a folic acid deficiency.

DR. H. K. FIDLER (Pathologist).—It is difficult to establish a diagnosis in this case with absolute accuracy. I would like to comment upon the results of the bone marrow examination, which are particularly relevant. The term

"megaloblast" is used in the morphologic sense to designate that cell in the erythroid series corresponding to the abnormal cell found classically in the marrow of patients with pernicious anemia. Before folic acid therapy, the bone marrow revealed 5 per cent megaloblasts as well as macromyelocytes. Following treatment, all these cells had disappeared.

It is unfortunate that a better reticulocyte base was not established while the infant was on liver therapy. The failure to obtain an adequate response to parenteral liver may indicate a relationship to the so-called "archrestic" or "liver refractory anemia" of adults, in which folic acid therapy has shown a satisfactory response where liver has failed. The apparent lack of response to liver is in contrast to the majority of cases of infantile megaloblastic anemia reported in the literature.[1] We are justified in doubting the validity of specific reticulocyte response within twenty-four hours of commencement of therapy. However, the presence of megaloblasts in the marrow immediately before institution of folic acid therapy and after one month of liver therapy satisfies me that liver was ineffectual. I believe that this case is best classified with the group of macrocytic anemias of infancy, first reported by Zuelzer and Ogden[1] in 1946.

DR. REGINALD WILSON (Associate in Paediatrics).—We have presented this case as an atypical anemia in a premature infant. This infant had an anemia more severe and more rapid in development than is usual in the simple anemia of prematurity. The evidences of hemolysis, megaloblastic marrow, and splenomegaly also differentiate this case from the anemia usually seen in prematures. In the differential diagnosis one must also include:

1. Congenital hemolytic anemia (acholuric family jaundice). Fragility tests on the child and both parents excluded this.

2. Lederer's anemia. The age of onset and other clinical features such as fever and prostration described in Lederer's anemia were not present in this case.

3. Von Jaksch's anemia. This syndrome may well have included cases similar to ours. However, hemolytic anemias due to many other causes were also included in the classification described as "anaemia pseudo leucaemia infantum."

4. Syphilis and infection were excluded.

5. Megaloblastic anemia of infancy (Zuelzer).

This case has many features in common with the syndrome described by Zuelzer and Ogden, in that it developed a severe macrocytic anemia, the marrow was megaloblastic, folic acid gave a prompt reticulocyte response, and after this treatment the marrow returned to normal. However, the cases they described were in older infants, there was often an associated infection, and liver *or* folic acid produced a reticulocytosis.

In conclusion, I would like to point out, from our study of this patient, that hemolysis in the newborn premature infant will apparently exhaust the supply of certain essential hemopoietic factors and lead to a nutritional macrocytic anemia.

DR. DONALD PATERSON (Senior in Paediatrics).—Frankly, I was not previously aware of cases of this type. Zuelzer's work has emphasized that nutritional factors are involved in some of the macrocytic anemias of infancy. I have been interested in the presentation of this case, which illustrates a similar process.

Although I am assured that there was no evidence of Rh incompatibility in this infant, I am not satisfied that our knowledge of this factor is sufficient to say that it could not be operating here. Could this be a missed case of mild erythroblastosis? I would like to know if the genotypes have been checked and I would also like to know something regarding the child's present condition.

DR. REGINALD WILSON.—This child has been re-examined at the age of one year. He is normal hematologically, physically, and developmentally. There is no change in the Rh picture. The spleen is still enlarged.

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Case 2. Chronic Pyuria (Congenital Defect) Presacral Sympathectomy (Final Report of a Previously Reported Case)

DR. E. LEHMAN (Assistant Resident in Pediatrics) for DR. A. F. HARDYMENT.—Miss P. C., a white girl aged 15 11/12 years at the time of her death in November, 1948, was the subject of a report in the JOURNAL[1] when she was 14 months of age. At that time she had had a left presacral sympathectomy done in an attempt to relieve a demonstrated left hydroureter with reflux from the bladder on that side. There was x-ray evidence of some degree of hydronephrosis on both sides preoperatively with some reflux from the bladder to the right ureter also (Fig. 4). However, postoperatively it was felt that "there was decrease in size of the bladder and ureter."

The child was presented at that time as "a case of persistent pyuria due to a neuromuscular dysfunction of the bladder for which a presacral sympathectomy was done." No obstructive lesion was found anywhere in the urinary tract.

On discharge from the hospital, two months after the operation, the urine contained *Bacillus coli,* a faint trace of albumin, and 1 to 2 white blood cells per high power field.

It would appear justified to report the progress of this girl during her remaining years and the remarkable findings at autopsy.

Approximately seven months postoperatively her urine showed 4 plus white blood cells with clumping, a very occasional granular cast cell and red blood cells. *B. coli* were cultured from the urine.

In 1935, grand mal type seizures began, continued during the next five years, and ceased without explanation during early 1940. During this time she had many attacks of "pyelitis." In March, 1940, several examined specimens were clear.

In November, 1943, she was reported as having no convulsions, was sociable but irritable, and was not doing well at school. At this time she had pyuria which was controlled by sulfonamide and mandelic acid.

In December, 1946, the urine showed albumin from a trace to 2 plus, and a few pus cells. She was "slightly anemic."

In March, 1947, the pyuria was reported as not responding to the sulfonamide and mandelic acid. *B. coli* were cultured from the urine.

In November, 1947, a year before her death, she was investigated in the hospital. A Mosenthal test showed specific gravity from 1.009 to 1.011; hemoglobin, 70 per cent (9.11 Gm.); leucocyte count, 3.800; nonprotein nitrogen 50. Catheterization of each ureter showed 4 plus pus on right side and 2 plus on left side. No organisms were grown.

Fig. 4.—Pyelogram, Jan. 16, 1934.

At each visit above noted, blood pressure readings were attempted but the results were never considered to be accurate because of the attitude of the patient.

In July, 1948, there is a report that "the patient has grown into quite a tall, young girl, rather nice looking, but is immature emotionally and requires patient and consistent encouragement at school; otherwise her progress is satisfactory, is very introspective and has a feeling of insecurity as to her own ability."

In September, 1948, when first seen by us, she was reported to have recently developed a violent temper and no interest in her personal appearance. She

complained of occasional headaches relieved by Aspirin. For two weeks she had had frequent nausea and vomiting. On Sept. 28, 1948, urine showed albumin 3 plus and an occasional white blood cell. Hemoglobin 52 per cent (6.76 Gm.), red blood cells 3,000,000, white blood cells 5,400, sedimentation rate 82 mm. in one hour; nonprotein nitrogen 103, blood pressure 148/70, pulse 98, temperature 99.1° F. Scattered rhonchi were heard in the chest. Chest x-ray was negative. She was admitted to the hospital September 30.

A Mosenthal test showed fixed specific gravity of 1.010. The fundi showed mild edema with a fresh, small hemorrhage on the right side.

She was noted to have a positive Chvostek's sign, uremic breath, an enlarged heart, and sacral edema.

On Oct. 24, 1948, massive subconjunctival hemorrhages developed. Copious vomiting was present. All treatment was of no avail; i.e., no diuresis was produced.

On Nov. 1, 1948, violent convulsions occurred. Terminally the patient was deeply unconscious with edema of the extremities. On November 6, nonprotein nitrogen was 167. She expired on Nov. 11, 1948. Plasma chlorides were 540 mg. per 100 c.c. on October 20 and 492 mg. per 100 c.c. on October 30.

Fig. 5.—Gross appearance of kidneys and ureters. Note large circumscribed nodule of fibrous tissue in left kidney.

Dr. H. K. Fidler (Pathologist).—The post-mortem examination was carried out twenty-three hours after death. The right kidney weighed 60 grams and the left 30 grams (normal 100 to 150 grams). Each kidney was small, markedly distorted, nodular, and firm in consistency. The capsule stripped with difficulty, causing some decortication. The cut surfaces showed moderate dilatation of

pelvis and calyces. The cortex was reduced to a narrow zone about one-half normal thickness and much of the corticomedullary differentiation was lost. In each kidney there were several circumscribed nodules of pale, yellowish-brown, homogeneous tissue of soft, fibrous consistency, measuring up to 2 cm. in diameter (Fig. 5). The ureters were dilated to about twice normal size and their walls were quite thickened (Fig. 5). The ureteric orifices in the bladder showed normal patency and the bladder appeared essentially normal.

The heart was enlarged, weighing 300 grams, and the left ventricle measured a maximum of 13 mm. in thickness. A small amount of atherosclerosis was noted in the aorta.

Each lung weighed approximately 540 grams (normal 300 to 400 grams) and showed patchy, pneumonic consolidation of the lower lobes.

Microscopic examination confirmed the impression of chronic pyelonephritis. There was marked destruction of glomeruli and tubules with replacement by fibrous connective tissue and a chronic inflammatory infiltrate.

The circumscribed nodules seen macroscopically proved to be loose, fibrous, connective tissue containing only scattered atrophic tubules. The ureter showed marked submucosal fibrosis but the muscle layers appeared essentially normal. Sections of the lung confirmed the diagnosis of bronchopneumonia.

No conclusion can be reached concerning the primary etiology of the renal lesion other than the fact that it was not on the basis of any organic obstructive lesion of the urinary tract. It would be consistent with a neuromuscular dysfunction in which chronic bacterial infection resulted in marked destruction of renal tissue causing renal decompensation and hypertension.

DR. H. L. CHAMBERS (Assistant in Urology).—This case presents the typical clinical and pathologic picture usually found in the condition commonly called "megalo-ureter" or "congenital idiopathic dilatation of the ureter." That is, it shows marked dilatation of the ureter with gaping orifices and without any demonstrable mechanical obstruction.

The etiology is still not settled. It may be due to some disturbance in the neuromuscular control of the ureter and bladder. Other possible causes that have been suggested are hypoplasia of the musculature and absence of the normal inhibition of ureteral growth at the fifth month of fetal life.

The treatment of megaloureter is difficult. A left presacral sympathectomy was done in this case, no doubt on the theory that the sympathetic supplies inhibitory fibers to the detrusor and motor fibers to the internal sphincter and smooth muscle of the proximal urethra. This might contribute to the dilatation of the bladder and ureter. However, the actual role that the sympathetic and parasympathetic systems play in ureteral function is not definitely established. Lapides,[2] in a recent report on the physiology of the human ureter, found that ureteral peristalsis and tone were not affected by blockade or by stimulation of the sympathetic and parasympathetic nervous systems. Thus he concluded that the ureter is an autonomous organ. If this be so, it is difficult to understand how sympathectomy has anything to offer these cases. At any rate, it is apparent that the procedure was of very little, if any value in the case under discussion.

DR. DONALD PATERSON (Senior in Paediatrics).—I think that this case was typical of the end result in long-continued pyelonephritis which was obviously bilateral. Over the years these cases have demonstrated that quite considerable periods are common when the urine might be clear and no fever present, then bouts of fever with pus occur, almost certainly due to miliary renal abscesses draining into the pelvis of the kidney. The final result, namely, bilateral renal fibrosis with uremia and high blood pressure, is typical of such a renal lesion. The lesson to be learned is for the condition to be diagnosed and strenuously treated with modern antibiotics. A month's or two months' treatment might be necessary at the onset. Where the infection is confined to one kidney due to a malformation, nephrectomy would result in a cure. A sedimentation rate is an extremely valuable aid in ascertaining the cessation of such a renal infection.

DR. A. F. HARDYMENT (Assistant in Paediatrics).—Through the years that passed between the operation on this child and her death, many efforts were made to control her infection. Sulfonamides and antibiotics were not available during the earlier years. Later on there was little, if any, cooperation with the attending pediatrician. At any rate, infection finally completely destroyed her kidneys.

If we see such a case today with bilateral megaloureter, we can only attempt to control the infection. If the condition is unilateral we must remove the infected kidney. The present case illustrates the fact that presacral sympathectomy is not of value in relieving the condition.

This is a final report on a previously reported case.

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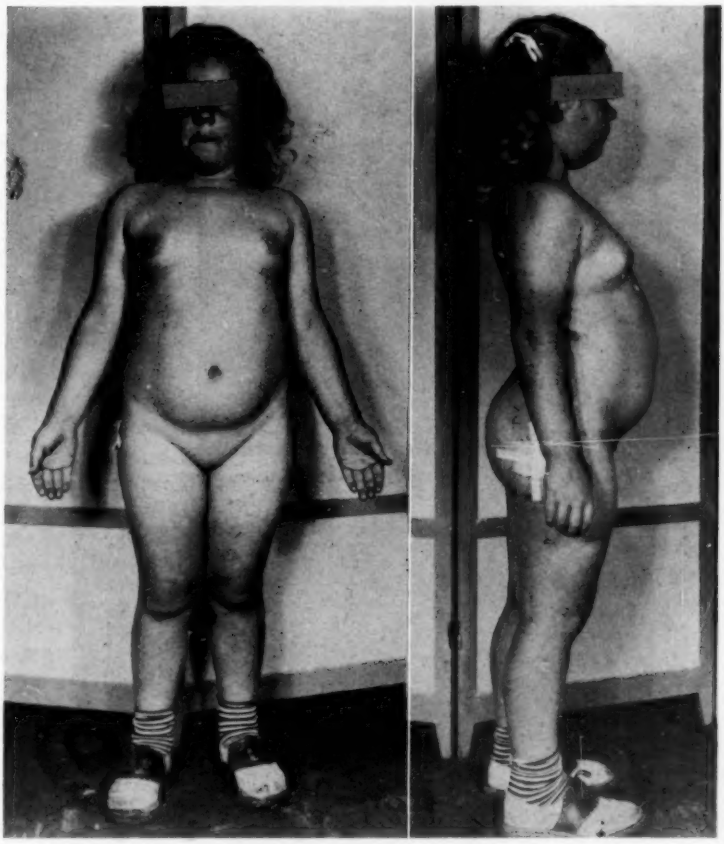
Case 3. A Case of Polyostotic Fibrous Dysplasia (Albright's Syndrome)

DR. A. MALKIN (INTERN), FOR DR. JOHN PITERS.—This patient (M.G.) is a white female child 5½ years old who was admitted to the Vancouver General Hospital on May 30, 1948, with the complaint of vaginal bleeding. She had been well up to May 20, ten days prior to admission, when she developed crampy abdominal pain which persisted on and off for the entire day. The following morning she began to have vaginal bleeding which continued for about one week, requiring the use of several napkins daily and being fairly typical of a normal menstrual period. The flow had ceased by the time of admission. The mother was also concerned by the patient's increasing obesity. She had always been a large and sturdy child, enjoying good health and showing better than average intelligence, but for the past eighteen months she had seemed hungry all the time and had become markedly obese. She was troubled frequently by enuresis. It was elicited that a wood tick had been removed from the back of her head on May 17 and another found partly embedded and removed on May 23.

The patient's birth history and early development were normal. The past history was negative except for frequent attacks of tonsillitis. The family history was essentially negative. There are three male siblings, all apparently normal in stature and appearance. There was no evidence of familial endocrine abnormality.



Figs. 6 and 7.—Front and side view of the patient.

Physical examination (Figs. 6 and 7) revealed a large and obese child, 48 inches tall and weighing 81 pounds. The breasts were enlarged with definite pigmentation of the areolae. This breast enlargement was partly due to increased fat deposition and partly to hypertrophy of the glandular tissue, which felt firm and seemed about 3 cm. in diameter. There was no pubic or axillary hair. The skin was normal in appearance except for a triangular, sail-shaped area of pigmentation in the left suprascapular area, extending laterally from the midline. This area measured 8 cm. in the vertical diameter and about 6 cm.

Fig. 8.—X-ray showing dysplasia in humerus and radius.

Fig. 9.—X-ray of hands showing dysplasia of bones.

at the base. The pigmented skin was not elevated. The scalp, eyes, ears, and nose were essentially clear. The tonsils were markedly enlarged and cryptic. Three of the 6-year molars and the two lower permanent incisors were present. The heart and lungs were negative. The blood pressure was 104 systolic and 74 diastolic. The spleen was barely palpable. The genitalia showed slight but definite enlargement. The nervous system showed no abnormalities.

The laboratory investigation was as follows: urine analysis, negative; red blood cell count, 4.2 million; hemoglobin 76 per cent; blood calcium, 10.7 mg. per cent; blood phosphorus, 6.4 mg. per cent; alkaline phosphatase 19.7 Bodansky units; nonprotein nitrogen 24 mg. per cent; cholesterol, 143 mg. per cent; fasting blood sugar, 99 mg. per cent; glucose tolerance test following 70 Gm. of glucose orally showed a rather flat curve; the 17-ketosteroid excretion was recorded as 0.744 mg. of androsterone per day; stained vaginal smears showed a typical postmenstrual appearance.

The x-ray examination of the skull, spine, and ribs was negative. The pituitary fossa was within normal limits. Some definite change was noted in the upper end of the shaft of the left radius (see Fig. 8), where the normal architecture has been replaced by an amorphous appearance. There is a suggestion of an amorphous type of change in the left ulna and in the medial half of the lower end of the left humerus as well. The left hand (see Fig. 9) shows marked broadening of the shafts of the metacarpals throughout, with great thinning of the cortex and irregularity of architecture consisting of absorption of some and increase of other striae. The middle phalanges of the index and ring fingers show very marked broadening of the shaft with a uniform amorphous appearance of the bone. The proximal phalanx of the ring finger shows a somewhat less pronounced but somewhat similar appearance, with a combination of rarefaction as well. The distal phalanx of the ring finger is grossly broadened with quite a wide tuft so that its volume is probably twice that of the corresponding phalanx of the other hand. The right hand is relatively normal but the first metacarpal shows a broadening of the shaft with some irregularity of the architecture. The proximal phalanx of the thumb shows a somewhat similar change. The development of the hands resembles that of a child nearer 12 years of age than 6. The right humerus shows a very slight thinning of the cortex in the middle third of the shaft. The femora, tibias and fibulas show only a number of horizontal nutritional lines.

Dr. John Piters (Attending Pediatrician).—This patient is an example of a clinical syndrome first described by Albright in 1937. While still referred to as the Albright syndrome, the newer name of polyostotic fibrous dysplasia is more descriptive and seems to have been generally accepted. In this condition bone lesions showing osteitis fibrosa are associated with areas of pigmentation of the skin and a generalized endocrine dysfunction. When the disease occurs in female children precocious puberty is an added feature. The bone lesions may be single or multiple, are usually predominantly unilateral, and frequently are segmental in distribution. The characteristic pigmentation is patchy, tending to appear on the same side and having the same segmental

distribution as the bone lesions. The endocrine dysfunction may produce effects such as premature osseous development and maturation, hyperthyroidism, or precocious sexual development. The skeletal lesions constitute the central feature of the disease and usually progress slowly to cyst formation with a tendency to spontaneous fracture.

In this case the bone lesions are early and could have been easily missed if one had not deliberately looked for them. The important clue which directed our attention to the skeletal system was the area of pigmentation in the left suprascapular region. The medial border of this area ended so evenly at the midline over a distance of some 8 cm., that it suggested the pattern of cutaneous nerve distribution. It is interesting to note that the most marked bone changes, (in the left radius, metacarpals, and phalanges) and the skin pigmentation occur in regions supplied by approximately the same lower cervical nerve roots. If these bone changes had not been discovered, several other diagnoses would have to be ruled out. The presenting feature of precocious puberty could have resulted from a granulosa cell tumor or cyst of the ovary. Here one might have palpated an enlarged ovary or discovered an unusually high level of excretion of urinary estrogen. In polyostitic fibrous dysplasia, estrogen excretion varies with the menstrual cycle and is within physiologic limits. One also would have considered a lesion in the region of the midbrain, with pituitary irritation and stimulation. However, this patient has no evidence of an intracranial lesion. Oddly enough, there is no record of sexual precocity ever arising as a result of an actual tumor of the pituitary gland itself, although such a change has been noted following either neoplastic or inflammatory involvement of the midbrain. Hyperparathyroidism frequently has been confused with the Albright syndrome because of the somewhat similar bone lesions. The normal serum calcium and phosphorus determinations rule out hyperparathyroidism in this case. Hyperplasia or tumor of the adrenal cortex may produce early sexual development, but such changes tend to be heterosexual, with marked enlargment of the clitoris, early development of pubic and axillary hair, and other evidence of virilism. Our patient shows no masculinizing changes at all. She does show obesity of a marked degree. This is probably on the basis of pituitary dysfunction, although it has been suggested that the pituitary acts through stimulation of the adrenal cortex with overproduction of a so-called S-hormone.

Dr. Harrison, would you like to discuss the x-rays in this case?

DR. BEDE HARRISON (Chief of Department of Radiology).—The osseous lesions are visible bilaterally but they are more prominent on the left side. They are of three types: (1) There appears to have been complete absorption of lime, leading to a cystic appearance, the cysts being irregular in outline and spread along the long axis of the bones. These are well exemplified in the case of the left humerus. (2) An amorphous appearance as though the lime, instead of being limited to the architectural striae, is diffusely scattered through the whole of the tissue, exemplified particularly in the case of the left radius. (3) Destruction of the horizontal striae with retention and increased visibility of the longitudinal striae, well exemplified in the upper end of the left ulna.

DR. J. PITERS.—Would you tell us how the bone lesions in this case can be differentiated radiologically from hyperparathyroidism?

DR. B. HARRISON.—In hyperparathyroidism the lesions are generalized. Here they are spotty in distribution. The distribution of these lesions as well as their varied character is indicative of a polyostotic fibrous dysplasia.

DR. J. DAVIES (Chief of Department of Pediatrics).—Dr. Fidler, can you tell us something about the pathology of this condition?

DR. H. K. FIDLER (Chief of Department of Pathology).—This case would appear to fulfill the diagnostic criteria for the syndrome first described as "osteitis fibrosa disseminata" by Albright[1] and later termed "polyostotic fibrous dysplasia of bone" by Lichtenstein.[2] The lesions in bone consist of solid fibroblastic hyperplasia which fills the marrow cavity, causing resorption of bone and thinning of the cortex, although no new periosteal bone is deposited. The lesion may be distinguished from osteitis fibrosa cystica by the frequent presence of small islands of cartilage and the absence of cyst formation, although radiologically the bone lesion may appear cystic. It is often difficult, however, to distinguish between these two lesions on histologic grounds alone. The clinical, biochemical, and x-ray findings in this case appear adequate to establish the diagnosis without resort to biopsy.

The etiology is unknown but it has been thought to be a manifestation of some underlying trophic disturbance, possibly related to pituitary dysfunction, or it may be the result of an embryologic defect of bone. Recently it has been suggested that the monostotic and polyostotic types of fibrous dysplasia are unrelated etiologically[3] although such an hypothesis begs the question when the cause of neither is established.

DR. WILLIAMS (Intern).—I would like to ask Dr. Eden how he interprets the estimations for serum phosphatase and 17-ketosteroids.

DR. J. EDEN (Chemical Pathologist).—The excretion of 0.744 mg., as androsterone in twenty-four hours is within normal limits for this age group and assuming that all urine voided during the collection period was saved, it indicates that the adrenal cortices are not oversecreting the hormones of which 17-ketosteroids are a degradation product.

The serum alkaline phosphatase level of 19 Bodansky units is pathologic in a child of this age, but high levels have been repeatedly reported in this disease and appear to be an integral part of the syndrome. The enzyme is elaborated by the osteoblasts and is concerned with the impregnation of the bone matrix with calcium salts.[4, 5] A high serum alkaline phosphatase level, therefore, can be interpreted as evidence of an attempt to repair or limit the lesions by increasing surrounding calcification. However, in this case the x-rays do not suggest any increase in the density of the bone surrounding the lesions.

More recently it has been suggested that the enzyme is mainly concerned with the formation of the fibrocollagenous framework of bone,[6] and so it is also possible that the elevated serum levels are the direct result of the overproduction of the fibrous matrix which occurs in this disease.

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Case 4. Cortical Carcinoma of the Adrenal Gland

DR. ELSA LEHMANN (Assistant Resident in Pediatrics).—This patient, G. W., a 17-month-old white boy, became feverish and listless two days before admittance to the Vancouver General Hospital on Sept. 28, 1948. During this time he could take only fluids, most of which he vomited. Because of these symptoms his family physician was called, who discovered a mass in the left upper quadrant and advised hospitalization.

Prior to this illness he had always been well and his parents had not noticed any change in his appetite or energy, nor did they consider that he had become paler.

Physical examination revealed a fairly well-developed and well-nourished child. His face was flushed and his eyes somewhat sunken. He whined continuously and appeared miserable. Temperature was 104° F., pulse 130, respirations 25, weight 11.3 Kg.

A mucopurulent nasal discharge was present. The pharynx was moderately inflamed. The ears, superficial glands, skin, respiratory, cardiovascular, nervous, and osseous system presented no changes.

The abdomen was flaccid and no tenderness was present. The liver and spleen were not enlarged to palpation. There was a large, firm mass about the size of a small grapefruit in the left upper quadrant extending from the costal margin to the level of the umbilicus, and from the flank to the midline; it was not tender and was only slightly movable. The external genitalia were of normal size and configuration and no pubic hair was present.

Laboratory Investigation.—The urine contained 1 plus albumin and 2 plus white cells in clumps. Red blood cells were 4.1 million; hemoglobin 11 Gm.; white blood cells 24,000 with a fairly marked shift to the left; platelets 269,000; nonprotein nitrogen 28 mg. per cent.

The patient was given 10,000 units of penicillin every three hours upon admittance, and two days later 5 grains of sulfadiazine every six hours in an attempt to clear up the urinary tract infection. After the first two days the temperature ranged between 99° and 100.6° F. Subsequent urinalyses were repeatedly negative.

An intravenous pyelogram was done on October 1, showing a large soft-tissue swelling in the left upper quadrant. Following the injection of the dye the right kidney appeared normal; the left, however, was displaced downward. The superior calices appeared normal in so far as visualized. Filling was not so complete as on the right, possibly due to pressure. The lack of gross de-

formity of the calices on the left suggested that the tumor was extrinsic, although the possibility of a tumor in the periphery of the kidney could not be excluded altogether.

On October 4 the patient was given a transfusion of 150 c.c. of whole citrated blood and the following day, under ether anesthesia, a well-encapsulated tumor of the left adrenal gland was removed through a left kidney incision without difficulty by Dr. George Langley. No metastases were visible at operation.

Postoperatively the patient received 250 c.c. of whole blood and 500 c.c. of normal saline intravenously. The immediate postoperative course was uneventful.

The pathologic specimen consisted of an encapsulated, fleshy mass measuring 9 by 9 by 4 cm. The outer surface was smooth and glistening, although somewhat lobular in appearance. The cut surface was composed of reddish-brown, soft, friable tissue.

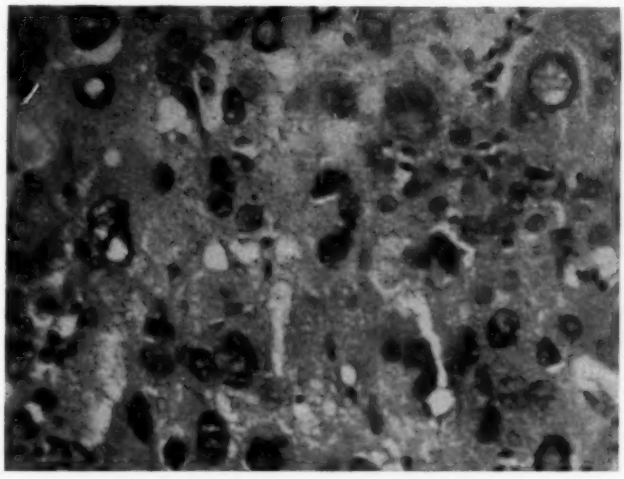

Fig. 10.—Section showing giant cells.

Histologic sections taken through the tumor mass revealed a sparse fibrotic stroma, supporting sheets of hyperchromic pleomorphic and polymorphic epithelial cells showing marked variation in size and shape, with numerous giant forms (Fig. 10). The nuclei were large and vesicular and contained numerous mitotic figures. The cytoplasm was sparse and in the larger cells was of an eosinophilic, granular nature. The stroma was heavily infiltrated with lymphocytes. The conclusion was giant cell carcinoma of the adrenal cortex.

Subsequent Course.—On October 18 deep radiation therapy was instituted, ten treatments being given between this date and on October 31. He was discharged on October 31 weighing 10.6 Kg.

Laboratory Data.—Red blood cells were 4.0 million; hemoglobin 9 Gm. per cent; white blood cells 5,000.

He was readmitted on Dec. 5, 1948, because of increasing pallor, lassitude, and abdominal distention. There was a general deterioration in his condition since he was last seen. He appeared paler and more irritable and presented a picture compatible with advanced malignant disease. The most significant change was the marked enlargement of his abdomen, which was due to a marked increase in the size of the liver. This organ extended into the right iliac fossa and was very firm and nodular in consistency. A moderate amount of ascitic fluid was present.

Laboratory Data.—Red blood cells 3.2 million; hemoglogin 6 Gm. per cent; white blood cells 15,000, of which 80 per cent were granulocytes.

The patient was removed by his parents after five days in the hospital, and died at home Dec. 29, 1948. No post mortem was granted.

DR. E. STEWART JAMES (Attending Pediatrician).—When this patient was first seen we thought the most obvious diagnosis was Wilms' tumor because of the size and location of the mass. After seeing the pyelograms which showed an almost normal kidney pelvis displaced downward, we thought the mass more likely to be extrinsic, probably adrenal, in origin. A Wilms' tumor, however, could not definitely be ruled out on this evidence. If the tumor were adrenal in origin it was thought that it was probably a neuroblastoma, because no signs of cortical dysfunction, such as virilism or Cushing's syndrome, etc., were present. Actually, an adrenal cortical tumor was not suspected, and for this reason the output of 17-ketosteroids in the urine was not measured. After we had received the pathologist's report we were a little uncertain as to what the prognosis would be, although we presumed it was very poor. Dr. Langley, as Dr. Lehmann has pointed out, was able to remove the tumor without great difficulty, and he saw no metastases. Following operation the patient received what was considered adequate radiation therapy. In spite of this the patient's course was rapidly downhill in the next two months, with marked metastatic enlargement of the liver.

DR. H. K. FIDLER (Pathologist).—The tumor in this child showed the histologic appearances of a malignant neoplasm. Two types of cell are seen, giant cells on the one hand, with abundant eosinophilic cytoplasm and extremely hyperchromatic nuclei, and elsewhere solid masses and irregular cords of small cells with relatively little cytoplasm but showing irregular and coarse nuclear chromatin structure. It is this small cell which is probably the more malignant in this tumor because several thin-walled blood vessels were found containing clumps of these cells (Fig. 11). Metastatic tumors would be expected ultimately in the lungs and possibly liver.

It is of interest to note the clinical lack of any hormonal activity. Such an association is common in the highly malignant tumors of the adrenal cortex but by no means invariable. In fact, the hormonal activity of the tumor cannot be determined with any degree of certainty by the degree of differentiation found.

DR. BEDE J. HARRISON (Radiolgist).—Giant cell tumors of the adrenal glands have been reported variously as being responsive and unresponsive to x-radiation, but in view of the fact that the adrenal cortex arises from the same anlage as the testis, I feel that these tumors should be given the opportunity that radiation affords. This patient, therefore, was treated along the lines laid down for treatment of the seminomas in that not only was the local tumor area irradiated but the glandular areas extending from the tumor as far upward as the neck were also included in the fields of treatment. However, the patient's blood picture rapidly deteriorated and treatment was ceased when he had received 1,000 r. When the question of further treatment came up he was discovered to have a large mass in the right upper quadrant, so no further treatment was given.

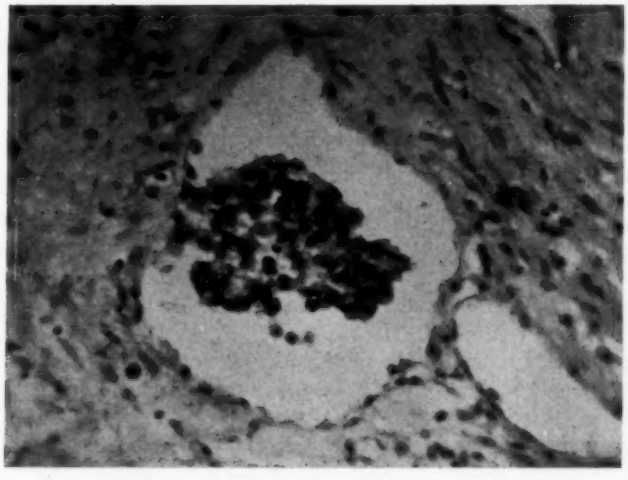

Fig. 11.—Clump of small type malignant cells in blood vessel.

DR. E. STEWART JAMES.—One assumes that this type of tumor must be quite rare, judging by most modern pediatric texts, in which little or no space is devoted to the subject, attention being focussed on those cortical carcinomas which are associated with sexual precocity, etc. The rapid deterioration of this patient to a fatal termination illustrates the point made by Dr. Fidler that cortical carcinomas in which hormonal activity is not in evidence clinically are usually highly malignant.

Psychologic Aspects of Pediatrics

THE HOME CARE OF THE PREMATURE INFANT

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NEWCASTLE-ON-TYNE is an industrial community in northeastern England with a population of about 280,000. Housing conditions in this busy mining town have been poor for a number of years; since the war they have deteriorated further. As in the rest of England, and the Continent as well, a large proportion of the babies are delivered in the home by trained midwives. Each year approximately 300 living premature infants (infants weighing 5½ pounds or less) are born in Newcastle-on-Tyne, somewhat less than one-half of these in the home.

In 1945 a program for the home care of premature infants was initiated. A corps of nurses was specially trained for this purpose and an ambulance service organized to deliver special beds, blankets, and other equipment, to the home if necessary. The maximum number of infants taken care of by one nurse is three; more usually she attends to two. Any medical practitioner may call for assistance by telephoning the maternity hospital.

Owing to the shortage of nurses, it was not possible for all premature infants born at home to have this specialized care and it has, therefore, been possible to compare not only the results of home and hospital care, but also the value of specialized over routine care in the home.

A preliminary report of the results for the first seventeen months appeared in 1947.[1] Recently the results of a three-year study have been reported.[2] During the entire three-year period 379 premature infants were born at home and 537 in hospitals. The over-all case fatality rate for those born and cared for in the home during the first twenty-eight days of life was 27.2 per cent and for the hospital group 19.5 per cent, a decided difference in favor of the hospital group. When, however, the home group receiving special care (159 infants) was compared with the hospital group, no difference in case fatality was found.

A comparison of the fatality rates by weight at birth of the babies born and specially cared for in the home in Newcastle-on-Tyne and those supervised in American hospital units[3] is shown in the chart. The American figures were compiled during the years 1940-1945 and are representative of the best results obtained in special premature stations. Unfortunately the British results have been expressed in pounds, the American in grams. Moreover, the British series is relatively small.

The results with the specialized care in the home strongly suggest that infants weighing 3½ pounds and over can, as a rule, be taken care of at home fully as well as in a special hospital premature unit.

Certain uncontrollable selective factors were operative in Miller's study, as is so frequently the case in studies with human material. For example, special aid was often sought for the small infants when there seemed to be a

chance for their survival, a factor which would favor the results in the group receiving special care. On the other hand, a factor operating against Miller's results was the fact that special nurses were often summoned when a larger infant was thought to require special attention.

Miller raises the question whether it is wise to attempt to provide hospital accommodation for all premature infants. It is his opinion that indiscriminate hospitalization for babies weighing over 3½ pounds is not warranted. Home care is not only safer from the point of view of infection and more economical; it has, in addition, he believes, a wholesome effect in promoting family ties and solidarity. This was not anticipated when the service was started but its significance and importance soon became apparent. Miller states: "The nurse in her role of teacher and adviser and by her personality mobilizes the family for duties: someone to watch at night; someone to watch during the day; someone, probably a neighbor, to shop; everyone interested is involved and all have a sense of achievement, which gives the child a good start and is far better than if he were taken away to a hospital and returned a month or six weeks later, an unknown infant, feared and strange."

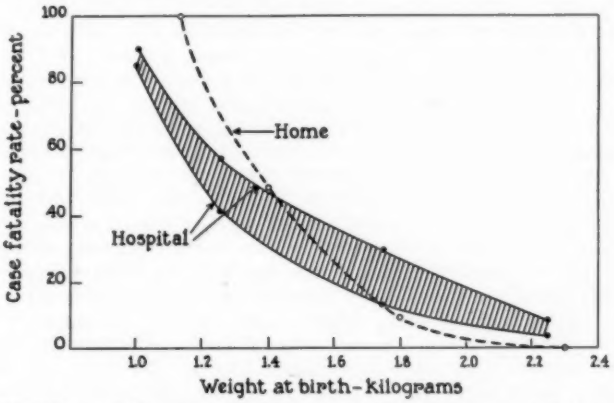

Chart 1.—Comparison of the case fatality of premature infants, specially cared for in the home and in hospital premature units.

The technique of caring for premature infants in the home with the help of specially trained nurses is one which requires careful consideration. If the larger infants who constitute a majority of the occupants of a premature unit can be taken care of at home, premature units will be relieved of a tremendous burden and more time will be available for the care of the smaller members. Moreover, a source of infection will be removed. In addition to the advantages enumerated by Miller, the psychologic trauma of separating parents and newborn infants will be eliminated and parental overanxiety lessened.

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Comments on Current Literature

ADVANCES IN ANTIBIOTIC THERAPY

CONSIDERING the phenomenal advance of knowledge concerning antibiotics within the past few years, it is not surprising to hear of major contributions in this field. However, two very significant contributions are reported in current literature which deserve special comment. In the March 25, 1949, issue of *Science*, Selman A. Waksman and Hubert A. Lechevalier[1] announced the isolation of neomycin, a new antibiotic active against streptomycin-resistant bacteria, including the tuberculosis organisms. Since 1939 Waksman and his associates have tested for activity against various bacteria many thousands of cultures, largely actinomycetes belonging to the genus Actinomyces (Streptomyces) which were isolated from soils, composts, peats, and other natural substrates.

Five years ago the isolation of streptomycin from *Actinomyces (Streptomyces) griseus* was announced. Since then streptomycin has proved itself invaluable in the treatment of a number of disease entities, and it has been especially important in the therapy of tuberculosis. However, certain serious limitations of streptomycin are well known, particularly its neurotoxic potentialities, and, on its prolonged administration, the tendency for the development of resistance among the infectious organisms. Favorable results obtained with dihydrostreptomycin, a reduced form of streptomycin, seem to indicate that the toxic reactions can be overcome, in part at least. The development of resistance among infectious organisms on prolonged administration of streptomycin constitutes a serious limitation, especially in the treatment of tuberculosis.

The isolation of neomycin from *Actinomyces fradii (Streptomyces fradiae)* is a major contribution to our knowledge since this antibiotic is effective not only in its action against many gram-positive and gram-negative bacteria, especially mycobacteria, but has been shown to be effective likewise in the treatment of known streptomycin-resistant strains. To date the toxicity of this new agent seems to be considerably less than that of streptomycin. The authors list several desirable properties of neomycin: "(1) similar activity against both streptomycin-sensitive and streptomycin-resistant bacteria; (2) considerable activity (in some cases greater activity than streptomycin) against various forms of *M. tuberculosis* and other mycobacteria; (3) limited toxicity to animals or none; (4) activity against various bacteria *in vivo*, including Gram-positive and Gram-negative organisms and against both streptomycin-sensitive and streptomycin-resistant organisms; (5) lack of resistance against neomycin among the organisms sensitive to it, or only limited development of such resistance."

With the isolation of neomycin a new opportunity for important advances in the treatment of human tuberculosis is presented, and clinicians will watch with interest for reports of the use of this newly isolated antibiotic.

Another significant advance in antibiotic therapy is described in a report by Joseph E. Smadel, Elizabeth Jackson, Herbert Ley, Jr., and Raymond Lewthwaite,[2] which appears in the February (1949) issue of the *Proceedings of the Society for Experimental Biology and Medicine*. This group of investigators present data resulting from careful comparative studies of the effectiveness in

rickettsial and viral infections of chloromycetin (chloramphenicol) from two sources: from fermentation liquor of cultures of *Streptomyces venezuelae*, N. Sp., and obtained by chemical synthesis.

The announcement by Crooks and his co-workers[3] that chloromycetin may be prepared synthetically is important news. Smadel and his group have shown experimentally that the effects of synthetic chloromycetin and fermentation chloromycetin are essentially identical on the rickettsiae of epidemic typhus, murine and scrub typhus, on those of spotted fever and rickettsial pox, and on the viruses of psittacosis and lymphogranuloma venereum. Chemotherapeutic studies of the two types of chloromycetin were carried out in embryonated hen's eggs and in mice. In each instance similar results were obtained with the two forms of the antibiotic.

A preliminary account of the effect of synthetic chloromycetin on patients with typical scrub typhus is presented. The response of these two patients following therapy was comparable to that observed in other cases of scrub typhus which had been treated with fermentation chloromycetin. The same low level of toxicity reported for fermentation chloromycetin holds true apparently for synthetic chloromycetin. In addition to the purely scientific importance of such a synthesis, it seems reasonable that synthetic chloromycetin will make available to clinicians a far greater supply of this remarkable antibiotic.

RUSSELL J. BLATTNER.

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2. Smadel, Joseph E., Jackson, Elizabeth B., Ley, Herbert L., Jr., and Lewthwaite, Raymond: Comparison of Synthetic and Fermentation Chloramphenicol (Chloromycetin) in Rickettsial and Viral Infections, Proc. Soc. Exper. Biol. & Med. **70**: 191, 1949.
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News and Notes

The **American Board of Pediatrics, Inc.**, announces the following dates for examination:

Written: Under local Monitors Friday, June 24, 1949.

Oral: Cleveland, Ohio, Sept. 16, 17, and 18, 1949.
New York City, Oct. 21, 22, and 23, 1949.
Chicago, Ill., Dec. 9, 10, and 11, 1949.

Dr. Henry W. Titus of New Rochelle, N. Y., died March 17, 1949. Dr. Titus had recently retired after forty years of pediatric pratice. He was formerly head of the pediatric service at the Grasslands Hospital.

Dr. James H. McKee of Philadelphia died March 25, 1949.

Dr. E. J. Huenekens, clinical professor of pediatrics at the University of Minnesota, has been appointed national medical director of the Kenny Foundation.

Dr. Harold K. Faber of San Francisco, professor of pediatrics and head of the department at Stanford University School of Medicine, will retire Sept. 1, 1949, and become professor emeritus. Dr. John A. Anderson, professor of pediatrics at the University of Utah, College of Medicine, Salt Lake City, will succeed Dr. Faber as professor of pediatrics at Stanford.

The **National Foundation for Infantile Paralysis** has issued the following "Message to Parents" for the 1949 season in case polio becomes epidemic in an area:

Avoid crowds and new contacts in trains, buses, or boats, if possible; avoid crowded places where you may be close to another's breath or cough.

Avoid over-fatigue; too active play, late hours, worry, irregular living schedules may invite a more serious form of the disease.

Avoid swimming in water which has not been declared safe by your health department.

Avoid chilling. Take off wet clothes and shoes at once. Keep dry shoes, sweaters, blankets, and coats handy for sudden weather changes.

Keep clean. Wash hands after going to toilet and before eating. Keep food covered and free from flies and other insects. Burn or bury garbage not tightly covered. Avoid using another's pencil, handkerchief, utensil, or food touched by soiled hands.

Call your doctor at once if there are symptoms of headache, nausea, upset stomach, muscle soreness or stiffness, or unexplained fever.

Consult your Chapter of the National Foundation for Infantile Paralysis for help. Your Chapter (see local telephone book or health department for address) is prepared to pay that part of the cost of care and treatment you cannot meet—including transportation, after-care and such aids as wheel chairs, braces, and other orthopedic equipment. This service is made possible by the March of Dimes.

A sound film in color has been produced at the University of Chicago on "The Function of the Ear in Health and Disease." It is edited by Drs. H. G. Kobrak, Joseph E. Hind, and Robert B. Miller. The film demonstrates the response of the ear to sound in health and disease, pathology, hearing curves in deafness, etc. It is available to universities and professional groups without charge through the Auralgan Research Division, 100 Varick St., New York 13, N. Y.

Book Reviews

The Thyroid and Its Diseases. J. H. Means, M.D., Jackson Professor of Clinical Medicine, Harvard University, and Chief of the Medical Services, Massachusetts General Hospital, Boston, ed. 2, Philadelphia, 1948, J. B. Lippincott Co., 559 pages. Cloth, price $12.00.

Eleven years ago the first edition of this book was generally accepted as the most comprehensive monograph available on the "Thyroid and Its Diseases," although the authors made no such claims as to its completeness. In the Preface of the first edition, the simple statement was made that "It is an account of the personal experiences of a considerable group of workers in a single thyroid clinic and of the opinions and convictions derived from this experience." The clinic was that of the Massachusetts General Hospital. In the intervening period of time the scope of this clinic has been broadened considerably by growth of personnel, liaisons with other clinics and institutions, and the contributions of competent workers from other countries who have spent appreciable periods of time at work in association with the clinic.

The second edition of this book again presents an excellent and comprehensive monograph on the subject of the thyroid gland. The general plan of the book is unchanged. Approximately the first third is again devoted to a review of the anatomy, nerve supply, biochemistry, physiology, and pathology of the thyroid, emphasizing the additional points of knowledge and suggestions derived from continued investigations, particularly with the use of the newer "tools" such us uptake of radioactive iodine and antithyroid drugs (thiocyanate, thiouracil, etc.). The chapter on Pathology of the Thyroid has been written by Rulon W. Rawson, M.D., Assistant Professor of Medicine, Harvard University. The interrelationship of the thyroid to other endocrine glands and to the body in general is stressed. The theory of the "thyroid-axis" is further supported and the site of the action of various therapeutic measures is explained on this theory. In the chapter on Methods of Examination in Thyroid Cases, attention is drawn to the history of goiterogenic foods and drugs, and the value of such diagnostic procedures as creatine tolerance, protein-bound iodine determinations, collection of radioactive iodine by the thyroid, and periodic bone-age determinations (in children). The measurement of the basal metabolic rate and blood cholesterol is, of course, included. The authors have altered somewhat their classification of disorders of the thyroid. The chapters on myxedema have been changed very little. The differentiation of primary thyroidal myxedema and anterior-pituitary myxedema (Simmonds' disease) is pointed out. Of special interest to the pediatrician is the importance, from a prognostic point of view, of the careful differentiation of the true cretin from the juvenile myxedema patient. The chapter on Graves' disease (thyrotoxicosis—old classification) contains adequate discussion of the newer types of therapy, such as antithyroid drugs and radioactive iodine, in addition to the established methods of surgery and iodine administration. Psychic trauma is ascribed only the "trigger" role in Graves' disease. The authors do not commit themselves to any fixed preference for a therapeutic measure, but wisely state: "At the present time, treatment must be individualized, and in each case the doctor must add the pros and cons of each type of treatment and decide which offers most to his patient."

The chapters on Tumors of the Thyroid, Thyroiditis, Anomalies of the Thyroid, Hypometabolism Without Myxedema, and Thyroid Administration in Diseases of Other Than Thyroid Origin, have been somewhat rearranged and brought up to date. The chapter on The Surgery of the Thyroid has been rewritten by Oliver Cope, M.D., Assistant Professor of Surgery, Harvard University.

L. D. THOMPSON.

Parent and Child. Catherine Mackenzie, New York, 1949, William Sloane Associates, Inc.

This book is a compendium of the articles written for the *New York Times* by an able and sincere journalist in the field of child-parent relationships. There is a difficulty, largely inherent in the enormity of the subject matter, which necessitates quoting isolated remarks from a multitude of authors. In the compact book form, this leaves the reader gasping a bit and one wonders whether it might not be less bewildering to parents if they were not confronted with quite such a parade of names. However, it is to Miss Mackenzie's credit that she is refreshingly honest in giving credit where it is due. She does not presume to give advice according to any preconceived ideas but reports the new developments in the field judiciously. The language is simple and forthright without being condescending. In spite of its local New York coloring, it is a book which parents all over the country will find useful.

M. E. BRANSCOM.

Maternity in Great Britain. London and New York, 1949, Oxford University Press, 252 pages. Price $4.00.

The report of a survey of the social and economic aspects of pregnancy and child birth undertaken by a Joint Committee of the Royal College of Obstetricians and Gynecologists and the Population Investigation Committee. This is a thorough, well-interpreted report of more interest to the obstetricians than the pediatricians. Conditions surrounding obstetrical care in Great Britain, where the midwife plays such an important role, are so different from practices in the United States that the report is more of interest than of value to American practitioners and students of sociology.

The Normal Child. Alan Brown, M.D., and Elizabeth C. Robertson, M.D., ed. 4, Toronto, 1949, McClelland and Stewart, Ltd., 274 pages. Price $3.00.

This is the fourth edition of Dr. Brown's book for mothers on the care of the baby and child. It has been entirely rewritten since the third edition which was published in 1932. It follows the general format of the many books on the subject. The text is clear and the revised edition is in keeping with modern practice and thought.

The Ciba Collection of Medical Illustrations. Summit, N. J., 1949, Ciba Pharmaceutical Products, Inc., 224 pages. Price $6.50.

For a number of years the Ciba Company has published and issued loose-leaf colored illustrations of anatomy and pathology by Frank H. Netter, M.D. One hundred ninety-one of these color plates have been bound together and are available at cost of printing. It is an excellent, well-printed book and the colored illustrations by Dr. Netter are far above average.

Current Therapy 1949. Edited by Howard F. Conn, M.D., Philadelphia, W. B. Saunders Company, 672 pages. Price $10.00.

This book on the "Latest Approved Methods of Treatment for the Practicing Physician" is a decidedly unique and interesting text. With an editorial-consulting group of twelve well-known medical teachers, over 200 physicians have contributed articles detailing the specific treatment of some 300 conditions. The text is confined to treatment and in some instances two or more authors have contributed methods for the same condition. The text is divided into fourteen sections as (1) the infectious diseases, (2) diseases of the digestive system, (3) diseases of metabolism, and so on, and includes dermatology, allergy, and obstetric and gynecologic conditions. The text is clear and printed in large type, making it easy to read. As nearly all of the methods have been contributed by men nationally looked upon as authorities in their special fields, the book should be of great value to the busy practitioner. The text, however, does not include many of the pediatric conditions which form such a large part of the practice of the general practitioner.

Editor's Column

FEDERAL AID FOR MEDICAL EDUCATION

IN VIEW of the controversy which has arisen over the question of Federal aid for pediatric education, it is pertinent to point out that the Federal government is allotting some twenty million dollars to medical teaching institutions for the fiscal year ending June 30, 1949. The bulk of this is for what is essentially graduate and postgraduate education.

In an address at the recent educational meetings in Chicago on February 7, Surgeon General Scheele of the Public Health Service stated that for the current fiscal year the Service had available a total of $24,427,000 to aid medical research and education. This expenditure is limited to certain specific fields of which cancer and psychiatry are examples. About eleven million dollars has been invested in research grants, eight million in construction grants, three million in fellowships and traineeships, and a little over two and one-quarter million in teaching grants. Grants for undergraduate teaching in cancer have been made to medical and dental schools. The March 12 issue of the *Journal of the American Medical Association* announced the allotment of $1,500,000 to forty-two medical schools for undergraduate teaching in psychiatry. Most of the schools will receive $12,500 a year for three years beginning July 1, 1949. Dr. Scheele stated that about 84 per cent of the total funds available for research and training has gone to teaching institutions. In addition to these funds, other sums have been allotted through the Children's Bureau to the medical schools for research and graduate training programs in maternal and child health. Thus the use of Federal funds for medical education is not a matter of ideological controversy but an accomplished fact. Let us say further that although we have been keeping an ear close to the ground, we have heard of no complaints of dictation of education policies by the government bureaus in the allotment of these grants.

The point we would like to raise is that although in a broad sense all this money is for medical education, as medical knowledge is dependent upon research, most of the money is being spent on the superstructure when the soundness of a program depends on the strength of its foundation. The foundation of medical education is the undergraduate teaching in the medical school, and this, from a financial standpoint, is the weak point in medical education today. Unless undergraduate education is sound, graduate and postgraduate programs of education and research based on Federal funds will inevitably fail in part to meet their objectives.

In the recently published survey of pediatric education which was reviewed in last month's issue of THE JOURNAL, Dr. John Mitchell presented some very illuminating figures in regard to undergraduate teaching as a whole and budgets for pediatric teaching. In twenty-five schools the budget for pediatrics is less than $50 per student, in twenty-five, between $50 and $200, and in twenty-five,

over $200. In forty-three schools the amount is less than $100 per student and in twenty-seven over $100. In five schools it is less than $10 per student per year, and in four, over $400.

The question that arises is why should there be such violent opposition on the part of some to Federal aid for undergraduate education when there is seemingly no opposition to the Federal government allotting about twenty million dollars this fiscal year to the teaching institutions for graduate and postgraduate education. It has nothing to do with the controversial subject of medical socialization, but is purely concerned with ways and means of improving medical care, which, in the final analysis, depends upon medical education. In much of the rather emotional discussion of medical care and economics which has taken place in recent months, the fact that good medical care is more dependent on the education and skill of the doctor than on the way in which he is renumerated for his services has been completely ignored by many taking part in the discussion.

The one and one-half million dollars recently allotted for undergraduate teaching in psychiatry went to only forty-two of the seventy medical schools. The basis of selection was where it was most needed and where it would do the most good. A similar sum for undergraduate pediatric teaching, divided among the schools which the survey has shown have inadequate budgets for good pediatric teaching, would be a sound investment for the children of the nation.

B. S. V.

STREET AND HIGHWAY ACCIDENTS IN 1948

THERE were 32,200 persons killed on the streets and highways in 1948. This is a decrease of 300 under 1947 but the number of nonfatal injuries reported jumped from 1,365,000 to 1,471,000. Of the 22,700 deaths resulting from the actions of drivers, 10,080 (44.4 per cent) were attributed to speeding. Of the deaths, 3,530 were in children under 14 years of age, a decrease of nearly 500 under 1947. Of the fatal accidents, 85.5 per cent occurred when the weather was clear, and 78.7 per cent when the roads were dry. Over one-fourth of the fatal accidents occurred in the late afternoon and early evening hours, 4 to 8 P.M. Saturday and Sunday were as usual the days with the highest rates and account for approximately 40 per cent of the total number of persons killed.